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Studies on the aetiology and pathogenesis of motor neuron diseases I. Lathyrism: clinical findings in established cases. A. C. Ludolph, J. Hugon, M. P. Dwivedi, H. H. Schaumburg and P. S. Spencer 149

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Alloaesthesia. Mitsuru Kawamura, Keizo Hirayama, Yoshikata Shinohara, Yoshiro Watanabe and Morihiro Sugishita 225

Arhinencephaly. The spectrum of associated malformations. Joyce A. Kobori, Marie Kaarsoo Herrick and Henry Urich 237

Book reviews 261

Forthcoming events 267

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Arhinencephaly. The spectrum of associated malformations. Joyce A. Kobori, Marie Kaarsoo Herrick and Henry Urich 237

Book reviews 261

Forthcoming events 267

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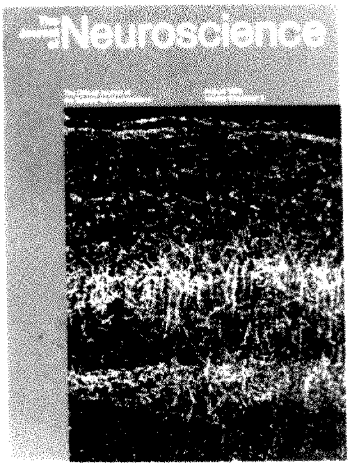

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ANALYSIS OF CEREBELLAR MOTOR DISORDERS BY VISUALLY-GUIDED ELBOW TRACKING MOVEMENT

2. CONTRIBUTION OF THE VISUAL CUES ON SLOW RAMP PURSUIT

by HIROKUNI BEPPU[1], MASANORI NAGAOKA[2]
and REISAKU TANAKA

(From the Department of Neurobiology, Tokyo Metropolitan Institute for Neurosciences and
[1]*Department of Neurology, Tokyo Metropolitan Neurological Hospital, Tokyo, Japan)*

SUMMARY

In visually-guided slow ramp elbow tracking, patients with cerebellar ataxia show irregular undulations of pursuit velocity which result in a position tracking pattern unlike the smooth constant velocity or rate tracking pattern of normal controls (Beppu *et al.*, 1984). This task provides ample opportunity to use both visual and proprioceptive feedback information for correcting errors. The present study investigated the role of visual information for generation of this saccadic pursuit pattern in the patients. A television screen was divided into upper and lower halves in each of which a vertical strip was displayed. The upper strip (*T*, target) was moved horizontally from the centre of the screen to the left or right by ramp voltage. The lower strip (*D*, displacement of the handle) was moved in proportion to angular displacement of the handle by a potentiometer coupled to the handle axis. The subject, while sitting in front of the screen, had to make *D* match the movement of *T* by controlling the handle with his arm. The range of *T* movement was 30 deg in terms of the angular movement of the handle. *T* velocity was 6.0 or 7.5 deg/s.

After a training session, the test was performed in which *D* or *T* was suddenly erased from the screen during pursuit, depriving the subject of visual information about the moving limb and/or performance. The procedure gave only minor effects on the performance of the control subjects, but it reduced significantly the velocity undulation of the patients with cerebellar ataxia, producing a smoother continuous pursuit. There were no significant differences in performance between *D* or *T* erase tasks. The result supports the hypothesis that the marked undulation pattern during pursuit movement in cerebellar ataxia is due to repeated visually-guided error correction responses. The relative importance of the visual pathway for conveying position information and the proprioceptive pathway for movement velocity information in this visual slow ramp tracking task is also discussed.

INTRODUCTION

In a previous study which comprised the first in the present series of investigations (Beppu *et al.*, 1984), the authors reported the basic movement patterns in patients

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with cerebellar ataxia on a visually-guided ramp-mode tracking task with elbow flexion. It was demonstrated that cerebellar defects are manifested both in slow and rapid precision movements. The latter defect has been well documented and is generally accepted as demonstrating the importance of the cerebellum in open-loop control of movements (Brooks and Thach, 1981). The former defect is represented, in particular, as successive undulations in saccadic velocity of arm movement during slow pursuit (*see* fig. 7, Beppu *et al.*, 1984). In clinical terminology, this type of undulation tends to be included in the category of 'cerebellar tremor'. The authors have already discussed the possibility that the pursuit pattern with velocity undulation in patients with cerebellar ataxia represents a *repetition of voluntary correction responses* for errors which are the inevitable outcome of the immediately preceding dysmetric catch-up responses, certainly not a form of involuntary tremor (*see* Holmes, 1939; Dow and Moruzzi, 1958; DeJong, 1979). It is certain that this undulation is caused neither by a primary defect in the motor system which generates a slow continuous movement nor by a disturbance in the sensory system which transmits visual and/or proprioceptive feedback information about arm movement to the CNS. The following findings support our argument: (1) subjects with cerebellar ataxia were able to move the arm fairly smoothly when allowed to move it at their own pace; (2) most of them had no sensory abnormalities; (3) the frequency of the velocity undulation was rather slow, ranging between 1 and 3 Hz, and showed some irregularity within as well as between trials; and (4) the movement did not take a forward and backward oscillatory pattern but rather a repeated forward movement and arrest response, that is, a staircase tracking pattern. This pattern is generally referred to as *position tracking* (*see* Poulton, 1974). In contrast, the tracking pattern in normal subjects for the same task is smooth with a fairly constant velocity which matches the target velocity and is referred to as *rate tracking* (for detailed discussion, *see* Beppu *et al.*, 1984).

The present hypothesis implies that error information is the major source of the undulation. In the light of this, it is interesting to ask what would happen to tracking performance if the visual cue on a television display, which conveys information as to the position and velocity of the target, the position and velocity of the handle in relation to arm movement, and the precision of the response, was erased during pursuit. In an attempt to answer this question, the previous methodology (Beppu *et al.*, 1984) was modified as described in the Methods section. A significant reduction of the saccadic undulation in arm velocity was revealed, supporting the present hypothesis.

METHODS

Subjects

Eleven patients with cerebellar degeneration (4 females, 7 males, aged 41 to 67 yrs) and 9 normal healthy controls (2 females, 7 males, aged 45 to 66 yrs) served as subjects. Both groups were matched in age distribution: 55.8 ± 9.0 yrs (mean ± SD) for the cerebellar ataxia group and 56.7 ± 7.8 yrs for

TABLE 1. CLINICAL DATA FOR PATIENTS WITH CEREBELLAR ATAXIA

ADL	Case	Age, sex	Duration of illness (years)	Diagnosis	Muscle tone	Tendon reflexes UL	Tendon reflexes LL	Pathological reflexes	Ataxia UL	Ataxia LL	Nystagmus	Sensory disturbance
A	1 (M.N.)	67, M	3	Cerebellar	↓	+	++	—	+	+	—	—
	2 (J.A.)	50, M	1	Cerebellar	↓	+	++	—	+	+	Horizontal	—
B	3 (H.I.)	65, F	2	Spinocerebellar	↓	+	+	—	+	+	—	—
	4 (T.K)	59, M	11	Cerebellar	—	++	+	—	+	+	—	—
	5 (H.K.)	49, F	3	Spinocerebellar	↓	+	+	—	+	+	—	—
	6 (N.M.)	46, M	2	Spinocerebellar	—	+	++	+	+	+	—	—
	7 (T.M.)	41, M	2	Cerebellar	—	+	++	—	+	+	Vertical	—
C	8 (B.A.)	65, F	6	Spinocerebellar	↓	++	++	—	++	++	Horizontal	—
	9 (M.T.)	63, M	5	Cerebellar	↓	+	++	—	+	++	—	—
	10 (M.S.)	60, M	9	Cerebellar	↓	+	+	—	+	++	Horizontal	+
	11 (T.S)	49, F	11	Spinocerebellar*	↓	+	++	—	+	++	Horizontal	—

ADL = activities of daily living; * hereditary; UL and LL = upper and lower limbs; normal range for tendon reflexes = +. Case 10, with sensory disturbances, had superficial and deep sensory impairment in the fingers and toes, but was normal in other areas including the elbow tested.

the control group. All subjects were informed as to the purpose of the research and experimental procedures in advance, and gave informed consent. Clinical data for the patients are summarized in Table 1. None of symptoms was severe enough to incapacitate patients from participating in the present tracking task. Nystagmus was not observed on forward gaze which was a requisite in the present task. The patients were classified into three groups (A, B, C) according to clinical severity, based on activities of daily living (ADL) scale. Group A cases showed mild disability but were capable of leading normal lives; group B cases showed moderate disability and were not able to work but could carry out some daily activities; group C cases showed severe disability and were unable to care for themselves.

All patients fully understood the present tracking task at the pretest explanation and were cooperative throughout the examination.

Apparatus and Methods

The arrangement of the apparatus and measurement system was the same as that in the previous study (fig. 1, Beppu *et al.*, 1984) and only a brief account will be given here.

A 14-inch colour television screen was divided into upper and lower halves, each of which displayed a vertical strip: an upper target cursor (*T*) and a lower control cursor (*D*). The latter was moved in proportion to the angular displacement of a handle moved by the subject's arm. In the tracking task, subjects were instructed to make the cursor follow the moving target which was driven at a constant velocity from the centre to the side of the screen with elbow flexion movement on the skillful side. The importance of accurate performance during pursuit movements was emphasized to the subject. The starting angle of the elbow joint was 90 deg and the range of the target movement was 30 deg. Subjects were familiarized with the task in a routine examination in which they were tested at target velocities of 7.5, 15 and 30 deg/s (*see* Beppu *et al.*, 1984). After subjects had demonstrated consistent performance in the preliminary task, the experiment proceeded to a task with visual cue erasing.

In the new task, special trials were introduced in which the control cursor was erased from the screen following an unpredictable delay of 1.0 to 2.5 s after the start of the tracking movement. Target velocities tested were 7.5 and 6.0 deg/s where duration of *T* movement was 4 and 5 s, respectively. These velocities were chosen because the duration of the pursuit phase was, on the one hand, too short for analysis at faster velocities and because, on the other, the usual rate tracking pattern tended to be replaced with a position tracking pattern even in control subjects on slower velocities (M. Nagaoka and R. Tanaka, unpublished observations). The control strip reappeared on the screen upon *T*-arrest at the end of the screen so that the subject could estimate his own performance in each trial (*knowledge of result*, *KR*). In some cases, the task without *KR* was tested, in which the control strip reappeared only when the subject regained the initial handle position for the next trial. Trials with the erased control cursor (*D*-ERS) were interspersed randomly among trials with the normal task keeping the visual cue (NRM). The subject could therefore not predict whether the forthcoming trial would be for *D*-ERS or NRM; 20 to 25 trials were repeated in one session, in which 10 were *D*-ERS trials. The initial 4 trials were invariably of NRM mode for reinforcing the subject's memory and performance of the tracking at the start of each session. In the *D*-ERS task, the subject was expected to continue the pursuit movement in spite of the absence of the control cursor. This task was originally designed for testing the contribution of kinaesthesia on slow pursuit movement (Nagaoka and Tanaka, 1981). In other experiments, the target cursor was erased instead of the control cursor (*T*-ERS).

Recordings were made for various movement parameters such as target signal (*T*), handle trajectory (*D*), velocity ($\dot{D}$), error ($T - D$), as well as for the EMG activitiy of the elbow flexor and extensor muscles (biceps brachii, brachialis and triceps brachii). They were recorded in parallel on an 8-channel recticorder (Watanabe Sokki, WTR-331-8L) and an 8-channel data recorder (Sony, DFR-3915). Lengths of velocity trajectories were measured from the paper records for calculation of weaving ratios (WR; *see* fig.3 and text for details) by a graphic digitizer with a resolution of

0.1 mm (OSCON, A4–10) which was connected to a 16-bit microcomputer system (NEC, PC-9801F). Amplification of the velocity traces as well as recording speed of the recticorder were set constant in all subjects, patients and controls, for standardized measurement of WR.

RESULTS

Sample records of visually-guided elbow tracking movements from a normal subject are shown in the left column of fig. 1. As stated before (Beppu *et al.*,1984), the visuomotor slow ramp tracking process can be divided into three phases: the *initial* catch-up phase (I-phase), the *middle* pursuit phase (M-phase) and the *terminal* arrest phase (T-phase). The present study is concerned specifically with the

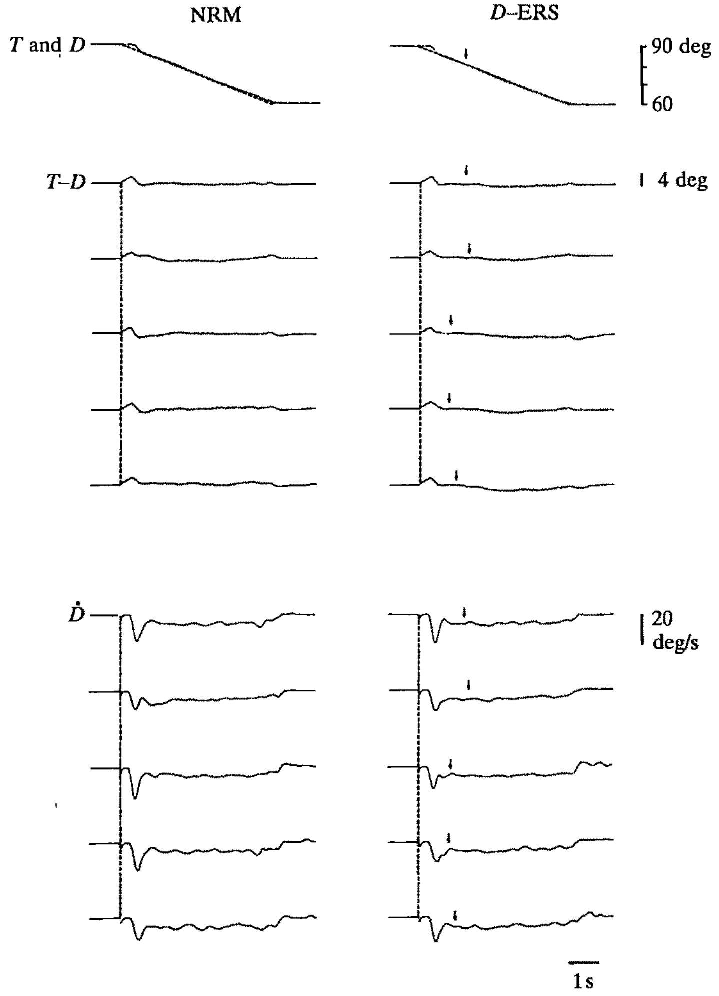

FIG. 1. Rastered records of velocity ($\dot{D}$) and error ($T-D$) trajectories on the tracking elbow flexion movement in a normal subject. The left column shows NRM trials while the right column those for *D*-ERS, in which the control cursor was erased from the screen (arrows) The control cursor reappeared on *T*-arrest.

M-phase. The accuracy of the tracking movement is clearly seen in the raster of the error traces (*T-D*) with only slight deviations from the base line. Traces of the handle velocity ($\dot{D}$) are also given in the raster record. Handle velocity was maintained at a fairly constant value and matched to the target velocity. This ensured that the control cursor matched the target cursor after a correct initial catch-up reaction. Some irregular undulations were observed, which were particularly obvious near the T-phase.

The results of *D*-ERS trials for the same subject are shown in the column on the right of fig. 1. Error traces followed the base line level fairly well and the velocity trajectory did not differ from that of the control records in the column on the left. Thus withdrawal of the visual cue for arm movement in normal subjects seemed

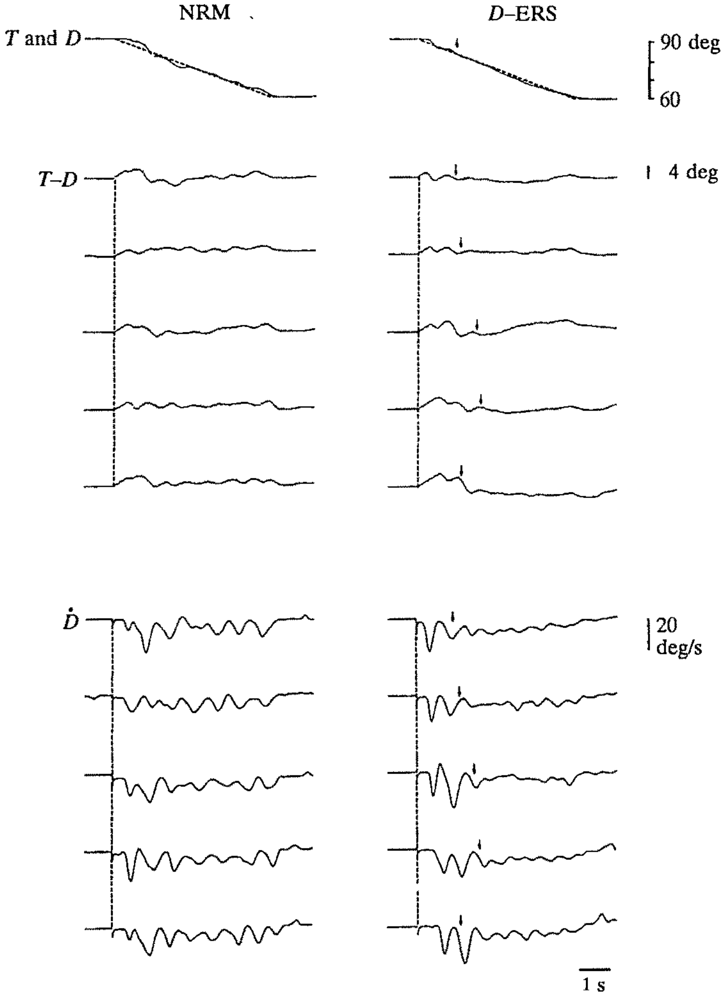

FIG. 2. Similar recordings as in fig 1, from a patient with cerebellar ataxia (*Case 11*, Table 1, *see* also fig. 8 in Beppu *et al*, 1984).

to have a negligible effect on the tracking pattern and precision, confirming a previous finding (Nagaoka and Tanaka, 1981).

Fig. 2 shows the results under the same experimental condition for a patient with cerebellar ataxia, the same subject as in fig. 8 in Beppu *et al.* (1984). Her ADL had deteriorated from B to C since the previous study. In the NRM session, her pursuit trajectory was again not smooth, showing an irregular stepwise tracking pattern which conformed to a position tracking pattern (fig. 2, column on left). Error records oscillated around the base line and the velocity records showed an irregular saccadic undulation, characterized as a *move and arrest* pattern. During *D*-ERS, however, the velocity traces showed a significant change to a smoother trajectory close to that of normal controls. Errors seemed to increase slightly towards the T-phase, but the extent of the error was not significant (*see* below).

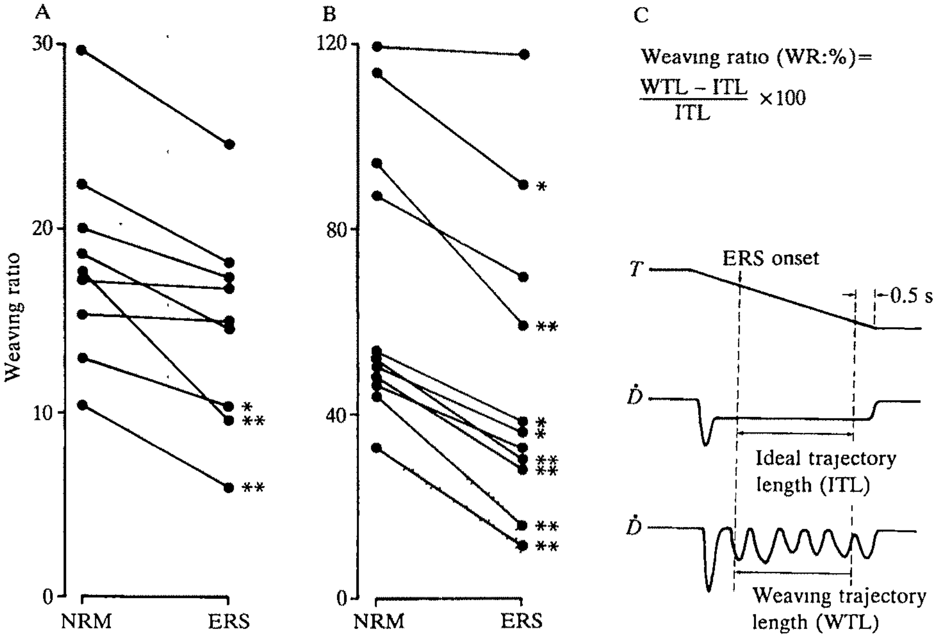

FIG. 3. Changes in the weaving ratio (WR) in *D*-ERS task. A and B are normal controls and patients, respectively. Note the WR scales in the ordinates are different in A and B. C shows the method of calculating WR, *see* text for details.

To estimate the degree of undulation in the M-phase in NRM and *D*-ERS quantitatively, the weaving ratio (WR) was calculated (fig. 3C). Duration of measurement on the handle velocity traces was between the onset of *D*-ERS and a point 500 ms before *T*-arrest. As explained in our previous paper (Beppu *et al.*, 1984), the latter point was arbitrarily chosen as the end of the M-phase. In an ideal pursuit, the velocity in the M-phase should be kept at a perfectly constant value matching the target velocity. Thus its trajectory is the shortest straight line parallel

TABLE 2 MEAN (SD) VALUES OF WEAVING RATIO AND ERROR

Case	*ADL*	*Age, sex*	*WR (NRM)* (%)	*WR* (D-*ERS*) (%)	*ERS/NRM*	*Error* (*NRM*) (*deg*)	*Error* (D-*ERS*) (*deg*)
2	A	50, M	32.5 (13.2)	11.2** (7.8)	0.34	−2.2 (0.3)	−2.8 (1.7††)
11	C	49, F	43.6 (19.2)	15.9** (7.7†)	0.36	−2.4 (0.5)	−3.4 (2.2††)
7	B	41, M	46.7 (23.3)	32.9 (7.5††)	0.70	−0.2 (0.7)	−1.2 (2.2††)
5	B	49, F	47.8 (8.2)	28.3** (8.2)	0.59	−1.3 (1.4)	−0.2 (3.6†) etc
4	B	59, M	50.5 (11.2)	36.1* (10.7)	0.71	2.4 (0.8)	4.3 (2.5††)
9	C	63, M	52.0 (12.6)	30.6** (9.6)	0.59	−2.1 (1.0)	−5.1 (2.0)
3	B	65, F	53.3 (12.4)	38.2* (11.1)	0.72	−2.8 (1.3)	−1.7 (1.7)
1	A	67, M	87.0 (37.0)	69.5 (16.8†)	0.80	−3.1 (1.5)	−0.8 (2.7)
8	C	65, F	94.7 (28.2)	59.2** (11.3†)	0.63	3.7 (1.0)	3.4 (3.5††)
6	B	46, M	113.3 (30.6)	89.2* (19.1)	0.78	1.9 (1.0)	0.3 (3.8††)
10	C	60, M	119.3 (34.7)	117.6 (25.7)	0.98	3.4 (2.0)	0.2 (2.6)
Totals							
Cerebellar (11 cases)		55.8 (8.6)	69.2 (36.3)	48.1** (34.4)	0.70	−0.3 (2.8)	−0.6 (3.7††)
Controls (9 cases)		57.7 (7.8)	18.1 (8.3)	14.6** (6.7†)	0.81	−1.5 (0.9)	−2.0 (2.0††)

Test target velocity = 6 deg/s. Asterisks indicate that the difference in mean values between the indicated value and the group on the immediate left is statistically significant (* $0.01 < P < 0.05$, ** $P < 0.01$). The t test or the Mann-Whitney U test were applied depending on the absence or existence, respectively, of a significant difference in their variances as determined by the F test († $0.01 < P < 0.05$, †† $P < 0.01$). Under Total, values were calculated from all the trials collected from all the subjects in each subgroup.

to the base line. The length of this hypothetical trajectory during the interval given above is defined as the *ideal trajectory length* (ITL). The actual pursuit trace inevitably showed an undulation, or weaving pattern, even in normal controls and the *weaving trajectory length* (WTL) was naturally longer than the ITL. The WR was calculated for each trial, employing the equation described in the figure. Thus the size of WR value is a function of the amount of undulation. The average WR value from ten *D*-ERS trials for one session with a target velocity of 6 deg/s is given in Table 2 as WR(*D*-ERS). WR of NRM trials was measured by the same method, but without the *D*-ERS procedure the onset of measurement was set to that of the mean *D*-ERS onset time as determined from the corresponding session. This procedure made it possible to compare the WR(NRM) to the WR(*D*-ERS).

In our previous study (Beppu *et al.*, 1984), we used a MAP (movement arrest period) ratio to estimate the degree of undulation. This indicated the summed period in which handle velocity decreased below some arbitrarily defined threshold regarded as a near arrest level, that is, 20% of the test velocity. This method was not adopted in the present study because it did not necessarily reflect smoothing of the handle velocity in *D*-ERS trials.

As shown in fig. 3A, mean WR(NRM) values were distributed between 10 and 30% and those for WR(*D*-ERS) between 6 and 25% in the normal subjects. The WR(*D*-ERS) and WR(NRM) distributions were significantly different in only 3 out of 9 subjects (*see* asterisks in fig. 3A). Although differences in the mean

WR(NRM) and WR(*D*-ERS) values were not statistically significant for the majority of the subjects, a highly significant tendency of reducing WR in *D*-ERS trials was revealed by the Wilcoxon matched-pair signed-rank test applied to the paired mean values for each subject. This was also verified by the Mann-Whitney U test on the data collected from all the control subjects. (Controls in the Total category of Table 2; the t test could not be used because the variance was significantly different between the two groups.) The ratio WR(ERS/NRM) was distributed between 0.55 and 0.97 (mean 0.81, SD ± 0.16). This finding indicates that, although the absolute amount of WR reduction appeared small, the visual information definitely contributed to the tracking performance of the normal subjects.

Fig. 3B and Table 2 show the results for patients with cerebellar ataxia. WR(NRM) exceeded the normal range in all cases and was widely distributed between 30 to 120%. The difference in distribution of WR(NRM) between ataxic subjects and normal controls was highly significant (Mann-Whitney U test, $P < 0.01$). WR(*D*-ERS) was distributed in a range between 10 and 120% which was also significantly larger than that of the controls ($P < 0.01$). Significant decrease in WR from NRM to *D*-ERS was shown in the majority of the cerebellar ataxia cases. In 2 (Cases 2, 11), WR(*D*-ERS) fell to values which were normal. The absolute amount of WR reduction, that is, the difference between WR(NRM) and WR(*D*-ERS), was much larger in the ataxic group than in the control group, due to a considerably greater WR(NRM) in the former group. The reduction also seemed to be greater in the ataxic group even in terms of the ratio WR(ERS/NRM). The ratios were 0.70 in the ataxic group and 0.81 in the control group (Total in Table 2), and the difference between the two groups, though appearing rather small, was highly significant ($P < 0.01$) when compared after normalization of individual data by dividing them by the mean for WR(NRM) in each group.

Unlike the MAP ratio, WR values appeared to be independent of the severity of disease (*see* Tables 1, 2), showing no relationship with duration, type, or clinical signs such as nystagmus and hypotonus. Fig. 4 shows the results for the 2 patients who indicated similar large WR(NRM) values, in spite of their marked difference in the ADL scale. It is clear that a large WR size can result from either a quickly repeated small position tracking (A) or a slow large one (B). In either case, the effect of *D*-ERS was obvious.

The *D*-ERS task also raises the interesting question as to whether the precision of performance is significantly affected. Since the terminal position of the *T* cursor on the screen and the angle of the elbow joint associated with it (30 deg) were familiar to the subject, the magnitude of errors at the time of *T*-terminal was measured as an approximate evaluation of performance. Hypermetric and hypometric errors were expressed by positive and negative values, respectively (Error in Table 2). The constant error, or the simple algebraic mean of the error, did not differ significantly between the patients with cerebellar ataxia and controls in either task nor between NRM and *D*-ERS trials in each subgroup. However, the variable error, or the SD of the error (bracketed numbers in Table 2), which best indicates

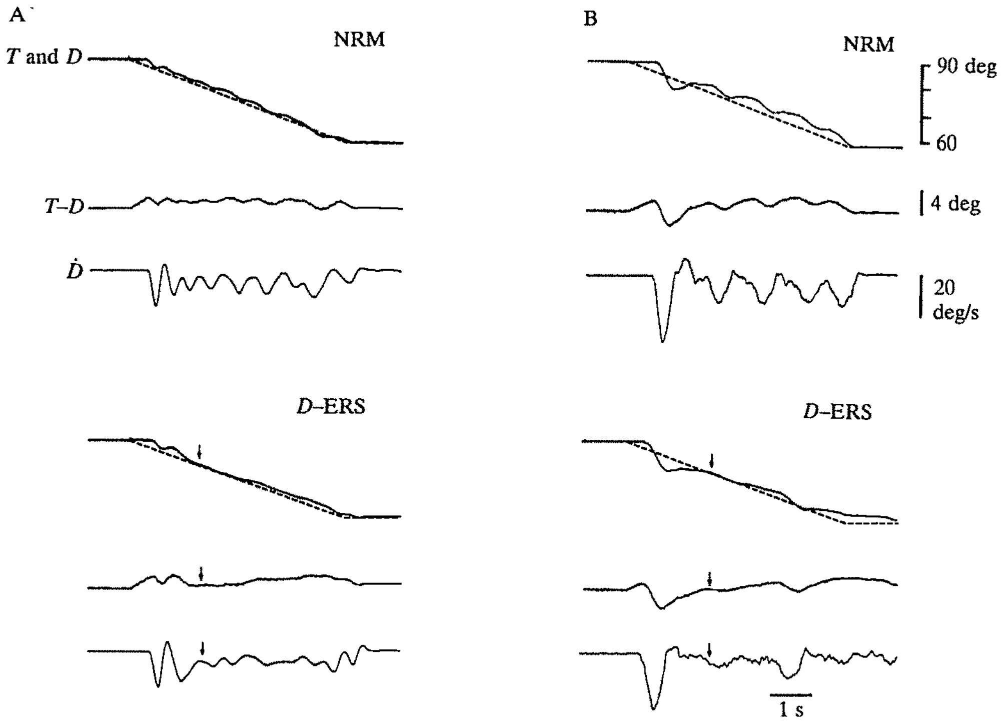

FIG. 4. Two typical tracking patterns with large WR values. A and B are undulations with higher frequency and small amplitude (*Case 1*, Table 1) and those with lower frequency and larger amplitude (*Case 8*, Table 1), respectively.

TABLE 3. EFFECT OF *KR* ON ERROR.MEAN (SD)

		+*KR*		−*KR*	
Case	*ADL*	*NRM*	D-*ERS*	*NRM*	D-*ERS*
2	A	−2.2 (0.3)	−2.8 (1.7††)	−2.3 (0.5)	−3.9 (1.2†)
11	C	−2.4 (0.5)	−3.4 (2.2††)	1.5 (0.5)	2.7 (2.4††)
6	B	1.9 (1.0)	0.3 (3.8††)	2.3 (1.4)	−1.2 (2.5)
8	C	3.7 (1.0)	3.4 (3.5††)	3.6 (1.5)	2.9 (3.8†)
Total		0.3 (2.8)	−0.8 (3.9†)	1.3 (2.5)	0.1 (3.9†)

Conditions as in Table 2. For further explanation, *see* text.

how well the subject is performing (Poulton, 1981), was larger without exception in *D*-ERS than in NRM sessions in normal controls. Increase in the variable error was much more remarkable in the patients. In this context, it might be argued that position and movement of the tested arm can be perceived in the subject's peripheral visual field and thereby somehow affect the result. This could have been the case in a few subjects who admitted on questioning that they often sensed their arm position by vision at *T*-terminal. However, when a partition was used for shielding their vision from the arm, performance did not change significantly.

The effect of the knowledge of result (*KR*) on precision of tracking performance was analysed in 4 patients (Table 3). The task without *KR* showed a similar extent of constant and variable errors to those of the task with *KR* revealing virtually no difference between the two tasks. This was also the case in normal controls.

The effect of *T*-ERS was also investigated in the 4 normal controls and 4 ataxic subjects. There was no apparent change in the pursuit response for this task compared with the preceding *D*-ERS task. Fig. 5 shows an example from a patient with cerebellar ataxia. The irregular velocity undulation pattern in NRM trials changed into a smoother pattern on withdrawal of the *T*-cursor. The extent of errors was similar to that of those in *D*-ERS.

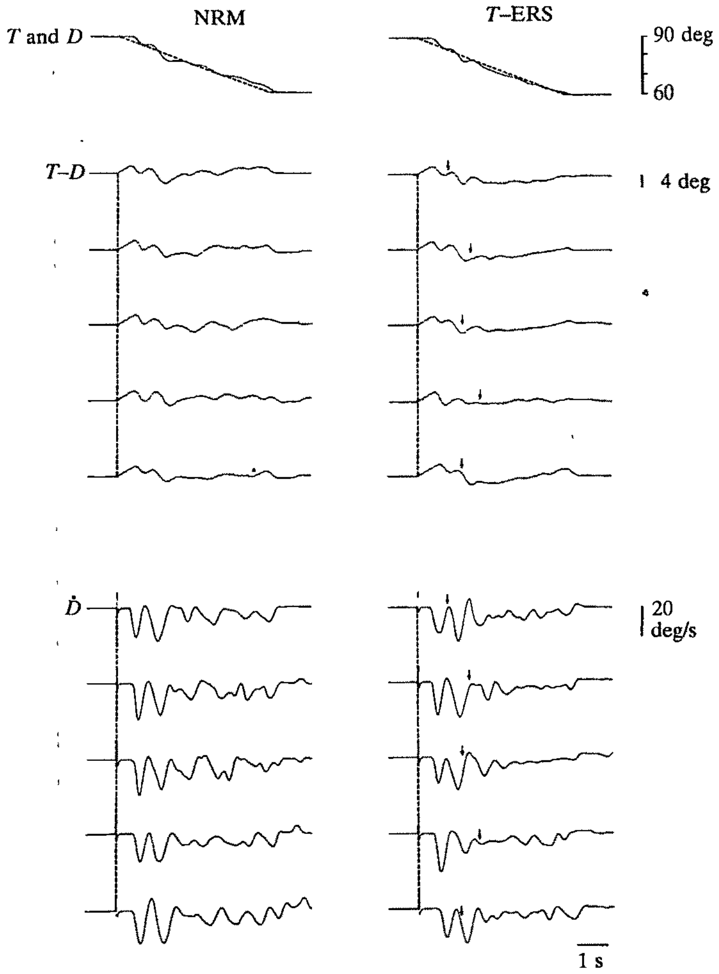

FIG 5. Similar recordings as in fig. 2, except that the right column indicates the effect of *T*-ERS. (*Case 2*, Table 1).

DISCUSSION

A salient feature of normal pursuit movement in a visually-guided slow ramp tracking task is that a constant handle velocity is maintained which matches the target velocity, resulting in a typical rate tracking pattern. In our preceding paper (Beppu *et al.*, 1984), we suggested that the realization of continuous precision pursuit requires the integrity of two basic mechanisms: a rough estimation with an open-loop control system and a fine corrective adjustment with a closed-loop system. In the latter system are included the visual and proprioceptive feedback pathways, both of which provide information about the performance of the moving arm. The movement-related information may be concerned with the position of the joint and the direction and velocity of the movement (*see* Burgess *et al.*, 1982). The direction information may be disregarded in the present study in which the task was preset to elbow flexion. The importance of the velocity information for smooth pursuit has already been stressed (Beppu *et al.*, 1984).

Origin of the Saccadic Pursuit Pattern in Patients with Cerebellar Ataxia

A feature of the experimental procedure adopted in the present study was the withdrawal of the control cursor from the television screen (*D*-ERS) during slow tracking. This task deprives the subject of the movement-related (position and velocity) information which is fed back through the visual pathway, thus forcing the subject to depend more on proprioceptive and/or central program mechanisms for performing an expected task. (Here, the term 'central program' is used to mean an entire sequence of motor commands for executing a certain intended movement which the CNS constructs and carries out with little influence from the feedback information generated by the movement itself.) The *D*-ERS effect is not limited to the loss of the movement-related information alone. Since the relative positions of the target and control cursors indicate the precision of performance, or degree of error, the *D*-ERS procedure also deprives the subject of error information. This should be kept in mind in the discussion which follows.

In the majority of the patients with cerebellar ataxia, the *D*-ERS procedure resulted in an obvious shift from a position to an approximate rate-tracking pattern, which is clearly shown in a quantitative way as a reduction of WR. This finding strongly suggests that visual cues play a crucial role in the generation of the velocity undulations seen in the patients. Which, then, is the more important factor in the present finding: position, velocity or error? The most direct answer to this question comes from an experiment in which the target cursor is withdrawn (*T*-ERS). The *T*-ERS task deprives the subject of information about the degree of error as well as the moment-to-moment instruction of position and velocity, but the movement-related information of the arm is still available from the control cursor. Because this task resulted in essentially the same reduction of undulation as the *D*-ERS task, it could be argued that the common factor between the two experiments, namely the error, is crucial. In other words, coexistence of both cursors is essential for generating the saccadic velocity undulation in the patients.

The present finding that the performance differed little between the *T*-ERS and *D*-ERS tasks does not necessarily indicate that both tasks had exactly the same effect. Most subjects, whether normal controls or patients, felt more uncertain of their performance in the *T*-ERS than in the *D*-ERS task, with a sensation that the handle had lagged appreciably behind *T*. This was realized to be an illusion from the *KR* given at the termination of *T* movement as confirmed by the authors when acting as subjects themselves. In general, greater attention in performance was required in the *T*-ERS than in the *D*-ERS test.

Separate Feedback Routes for Movement-related Information

The marked reduction of the saccadic undulation of the handle velocity in the *D*-ERS task sheds some light on the nature of information transmitted by the visual and proprioceptive systems. This reduction was also apparent, although small, in the normal subjects. Theoretically, both systems can convey information about joint position and movement velocity. However, we suggest that the visual system mainly supplies positional information and may provide only a secondary contribution to the velocity information. On the other hand, velocity information may be transmitted preferentially through the proprioceptive pathway. (It should be stressed that the term 'information' as used here is intended to mean that which is elaborated for an expected motor output and not simply a general term for perception.) This suggestion is based on the following reasons.

A prominent contribution of the vision for detecting errors of motor performance has been amply mentioned (Keele and Posner, 1968; Thomson, 1980; Poulton, 1981; Jeannerod and Prablanc, 1983). It is very likely that the error information transmitted via the visual pathway is categorically positional information concerning the difference between the *T* and *D* cursors. The larger variable error at the *T*-terminal in *D*-ERS compared with that in the NRM test seems to indicate that positional information is more easily processed by the visual system than by the proprioceptive system, at least in the present task of slow visuomotor tracking. To test the difference in acuity of the positional perception transmitted through the two pathways, a preliminary control experiment was carried out using the same apparatus and control subjects as those in the present study. A step-tracking task rather than ramp tracking was chosen so as to provide only positional information. A visual step-tracking task in which *T* and *D* cursors were maintained was compared with a task in which the *D* cursor was erased at the onset of *T* movement. This test was principally the same as the third task performed on wrist flexion movement in man by Sanes and Evarts (1984). While the constant error showed no significant difference, the variable error was always larger in the erase task, as was the case for wrist movement (Sanes and Evarts, 1984). Strictly speaking, this experiment may demonstrate the low resolution of the proprioceptive information or the inaccuracy of the proprioceptive memory of the target position to be matched, or both. We cannot at present decide which is correct. Nevertheless, the result clearly shows that, at least in the slow movement paradigm, positional information is processed in a much keener way through the visual system than the proprioceptive system (*see also* next section). It is also noted that the subject, whether patient or control, relies much more on visual than proprioceptive information when a visual cue is available.

If visually transmitted velocity information is available for motor control, the subject with sensory ataxia, in whom the proprioceptive pathway is interrupted while the CNS remains intact, ought to be able to perform a rate-tracking pursuit task normally. We have already shown that this is not the case for patients with sensory ataxia due to tabes dorsalis or to a cerebrovascular lesion confined to the thalamus (Beppu *et al.*, 1981; Nagaoka and Tanaka, 1981; Tanaka, 1984). In spite of their ability to perform an open-loop precision task correctly, as for normal subjects, they could not maintain a rate-tracking pursuit pattern. They showed irregular velocity undulations during the M-phase. This finding strongly suggests that the velocity information essential for exerting a smooth pursuit movement is fed back through the proprioceptive pathway from the moving limb. Experiments on behaving monkeys have revealed that the cerebellum receives feedback information related to movement velocity (Murphy *et al.*, 1975; Mano and Yamamoto, 1980).

The modality of the responsible sensory receptors is of further interest. Recent physiological studies have denied a major role for cutaneous and joint receptors in kinaesthesia. Instead, it has been proposed that the muscle spindle afferents are of major importance (*see* Burgess *et al.*, 1982; Matthews, 1982). Very recently, Hulliger *et al.* (1985) suggested from their microneurographic study on a slow ramp-tracking precision task with finger movements in man that muscle spindles provide information about the occurrence as well as the direction of slow isotonic movements at low velocities. So far they have tested only one velocity and thus it is not known whether the spindles also provide velocity information. It would be desirable to extend this type of experiment by using multiple velocities in an attempt to obtain a quantitative change in spindle activity at different velocities. On the other hand, spindle afferents did not show an accurate position response during active position holding (Hulliger *et al.*, 1982).

Tactics of Slow Ramp Pursuit Movement

If we accept the priority of the visual system for positional information and the proprioceptive system for velocity information, it seems easy to understand the tactics which normal subjects adopt for achieving the typical rate-tracking pattern. Any normal subject who was introduced to the present tracking task for the first time was able to acquire the correct rate-tracking pattern after a few early trials and to maintain it subsequently. This suggests that they learn very quickly that, after an accurate catch-up response at the I-phase, the pursuit response should ensure that arm velocity matches that of the target during the M-phase. This knowledge is constantly secured in an NRM session by feedback information as to the constant velocity from the arm preset to match the *T*-velocity, and minimum errors displayed on the screen. An error either in a hypermetric or a hypometric direction might at times be developed by a minor imbalance between *T* and *D* velocity. The subject, however, would quickly detect the error on the television display and adjust his arm velocity accordingly by a slight deceleration or acceleration depending on the polarity of the error. Such small undulations in the velocity trajectory are apparent in his performance as small WR values. On removal of the visual cue after a correct arm velocity was attained in the early stage of the M-phase, he would try to keep the velocity constant under the guidance of the velocity information supplied by the proprioceptive route and memory of the correct velocity. Thus the velocity trajectory tends to be a little more constant and straightforward. A small error increase at the terminal stage would be an inevitable result but it is still in a negligible range.

In contrast, visual information exerts a much more conspicuous effect on the performance of patients with cerebellar ataxia. Reduction of WR on *D*-ERS in the ataxic group by itself may not appear to exceed greatly that of the control group in terms of the WR(ERS/NRM) ratio, although the difference was statistically significant. However, absolute amount of background WR(NRM) and of reduction to WR(ERS) would be much more important for assessment of the actual output of motor performance. The patients can possibly perceive proprioceptive as well as visual information normally but cannot use this properly for computing forthcoming motor programs for correct responses both in well-timed and spatial ways, and are obliged to repeat dysmetric responses. A dysmetric initial catch-up response would provide another error to be corrected. The second response to counteract this error yields yet another error, and so on. It is well known that, in normal subjects, a corrective response for a visually presented error needs about 200 ms or a little more (Keele and Posner, 1968). It would be longer in patients with cerebellar ataxia who suffered from slowed reaction time, but stepwise pursuit with 1 to 3 Hz is in an acceptable range for this correction (Beppu *et al.*, 1984). With visual cues withdrawn, it is natural that the patients would be relieved from everpointing errors and, by substantially reducing corrective movements, to shift to a strategy with a more or less self-paced manner (*see* fig. 8 in Beppu *et al.*, 1984) for reaching the terminal position, thus converting the velocity trajectory to a straighter line.

Recently, Flament *et al.* (1984) reached an opposite conclusion from their experiments on monkeys. According to them, cerebellar intention tremor, which occurs when attempting to hold the arm in an intended position, is driven by stretch-evoked peripheral feedback and not by voluntary contractions based on vision. The discrepancy from the present results may depend mainly upon differences between the tasks that were employed. The test used by Flament *et al.* was a step movement with a large change in joint angle amounting to several tens of degrees at a very rapid velocity exceeding 100 deg/s. For such movements, the amount of proprioceptive information that is evoked may be very considerable and exert a greater effect. On the other hand, our paradigm is a slow ramp-tracking task with velocity of less than 10 deg/s, in which a mechanical change in the moving arm is gradual and small, and also requires moment-to-moment precision. In fact, activation of the Purkinje cells and those of the cerebellar nuclei reduces significantly on slow ramp movement compared with that on a step movement (Murphy *et al.*, 1975; Mano and Yamamoto, 1980). As for the inefficacy of visual information in the monkey experiment of Flament *et al.* (1984), the requirement for precision of response should be specified more clearly before a final conclusion is reached. Nevertheless, it would be of great interest to test a visual effect in a step-tracking movement in human subjects more systematically.

Overall, the present results are consistent with the hypothesis that the irregular velocity undulation during the M-phase is a repeated voluntary catch-up response for correcting the error which resulted from the previous response and was displayed on the screen.

Clinical Factors Affecting the Extent of WR

From the standpoint of the present corrective response hypothesis for the undulating tracking pattern in cerebellar ataxia patients, it is easy to explain why the extent of WR does not reflect the severity of the disease. The WR is a function of size and frequency of velocity undulation. Therefore, it is quite possible that a patient with milder disability who retains the ability to achieve a short reaction time, comparable to that of normal controls, produces a large WR by adopting a pursuit pattern of quickly repeated correction responses, although each catch-up response might be small in size. This was effectively the case in fig. 4A. Thus a simple comparison of WR size for scaling the clinical severity was not feasible. Generally, severer cases tended to display more the pattern shown in fig. 4B, namely a slower and larger undulation.

Precision of Pursuit

The effect of visual information was particularly apparent in the increase in the variable error in the *D*-ERS task which was seen both in normal controls and patients with cerebellar ataxia (Table 2). In spite of their motor disability, the constant error on *D*-ERS in cerebellar patients was surprisingly small. This fact might have given some investigators the impression that slow movements are less affected by cerebellar dysfunction. A significant increase in the variable error, however, shows the existence of dysmetria. The extent of the increase did not alter on removing *KR* (Table 3). These findings were in marked contrast to those of patients with sensory ataxia, who showed substantial increases in the constant as well as variable errors on *D*-ERS without *KR* (Nagaoka and Tanaka, 1981, and unpublished data; *see also* Rothwell *et al.*, 1982; Sanes and Evarts, 1984). It is likely that the patients with cerebellar ataxia, deprived of visually transmitted error information, will try to correct their performance by monitoring errors through the proprioceptive pathway, although this is less sensitive (*see* above), and endeavour somehow to reach the memorized terminal position with a reduced error. This consideration may partly explain the finding that, in some patients, the smoothed velocity trajectory in the ERS trials did not decrease to a level which corresponded to the self-paced movement. This sort of adjustment is surely denied to the patients with sensory ataxia who are at a loss without feedback information from the arm.

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ENCEPHALITIS LETHARGICA

A REPORT OF FOUR RECENT CASES

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SUMMARY

Four patients are described with an encephalitic illness identical to that described by von Economo. Electroencephalographic, evoked potential and autopsy data suggest that involvement of the cerebral cortex is more extensive than has been generally recognized. Serological tests and viral cultures failed to reveal the infectious agent but the presence of oligoclonal IgG banding in the cerebrospinal fluid in 3 of the patients during the acute phase of the illness would be in keeping with a viral aetiology.

INTRODUCTION

Accounts of febrile somnolent illnesses with residual apathy, ophthalmoplegia, chorea and weakness abound in the early literature. The Schlafkrankheit of 1580, Sydenham's febris comatosa of 1672-1675 in which hiccough was a prominent symptom, febre lethargica of 1695, coma somnolentium of 1780, Gerlier's vertige paralysante of 1887 and the dreaded Italian nona of 1889-1890, in which sleepiness, cranial nerve palsies and tremor occurred, are some examples of what may be a recurring plague caused by the same aetiological agent (Wilson, 1940; Sacks, 1982). Despite these historical forerunners, the sleeping sickness pandemic of 1916-1927 burst forth spontaneously in several different European cities unrecognized and then relentlessly spread around the world leaving an estimated half a million people dead or disabled. Constantin von Economo, however, relying in part on recollections of his parents' descriptions of nona, was able to show that what appeared as a series of unrelated polymorphous outbreaks was in fact a disease caused by a single transmissible factor. He delineated three main clinical presentations which seemed to breed true to form in local epidemics. The commonest variety, the somnolent-ophthalmoplegic form, started with an influenza-like illness which was followed by increasing drowsiness and confusion, then progression to continuous sleep, stupor and finally coma. External ophthalmoplegia, often with pupillary involvement, oculogyric crises and nystagmus were early features and some patients developed basal ganglia, cerebellar or upper motor neuron signs. A smaller number of people presented with bradykinesia, catalepsy and mutism (amyostatic-akinetic

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form), whereas a third hyperkinetic group mimicked acute catatonic schizophrenia with extreme motor restlessness, impulsions, visual hallucinations and dyskinesias.

Rapid debility with marked weight loss occurred in most patients and in the survivors convalescence was protracted, often with recrudescences. One-third of patients died in the acute phase, another third survived with chronic disability and the rest seemingly recovered (Yahr, 1978). By far the most destructive residual sequel was Parkinson's syndrome and some of those who had apparently recovered from the acute illness developed extrapyramidal symptoms after latent intervals of as long as twenty years. Others were left with sleep disorders, depression, obsessional ideation and repetitive motor behaviour.

The aetiology of epidemic encephalitis lethargica is unknown. At first exogenous toxins were thought to be important but subsequently an infectious cause was sought on the basis of epidemiological, clinical and pathological features. The agent was shown to pass through filters and the disease was transmissible to monkeys by injection of brain tissue from affected patients (von Economo, 1931). During the 1918 pandemic a number of authors also noted an illness, indistinguishable from that produced by inoculation with encephalitis lethargica tissue, could be produced in rabbits by subdural injection of herpes virus. Because the swine influenza pandemic occurred at the same time as encephalitis lethargica, some physicians have assumed a causal relationship (Ravenholt and Foege, 1982). The appearance of encephalitis lethargica, however, often showed no temporal relationship to the influenza and von Economo pointed out that half his cases occurred before the influenza epidemic. Although there are occasional reports of transmission of encephalitis lethargica (Wilson, 1940), the condition lacks the highly contagious characteristics of influenza and its spread throughout the world followed a different course (Weinstein, 1976). The isolation of influenza virus in 1931 and the further characterization of its properties militated against its being the cause of encephalitis lethargica. Gamboa *et al.* (1974) were unable to demonstrate antibody fluorescence to the swine strain of influenza A within the hypothalamus and midbrain of patients with postencephalitic Parkinson's disease. They did, however, show fluorescence to two other influenza A strains, NWS and WSN, in 6 patients with parkinsonism following encephalitis lethargica.

Four cases of encephalitis lethargica seen the The National Hospital for Nervous Diseases, London, between 1980 and 1985 are described.

PATIENTS

Case 1

Following a visit to the United States a 17-year-old West Indian girl became withdrawn, mute and childish and, over the next week, agitated, uncooperative and emotionally labile. Her mother commented that she had become 'fidgety' and drowsy by day and screamed uncontrollably throughout the night. A diagnosis of catatonic schizophrenia was made and she received electroshock treatment twice and was treated with haloperidol for two days before it was noted that she was pyrexial and had developed abnormal physical signs. On arrival at The National Hospital she was agitated and febrile

(38° C) and was having frequent oculogyric crises. There was marked sialorrhoea and between crises she uttered a repetitive obscenity and carried out stereotyped masturbatory movements. She exhibited occasional dystonic posturing but was able to follow and grasp to order. There was marked neck rigidity and bilateral optic disc swelling, the pupils were medium sized and responded to light and accommodation, external ocular movements were unrestricted with no nystagmus. All four limbs were rigid and she had bilateral grasp reflexes. She continued to show dystonia even when not in oculogyric crises and the breathing pattern was irregular.

She was severely dehydrated with prerenal uraemia which resolved with appropriate rehydration. However, she also developed disseminated intravascular coagulation which persisted for three weeks; this eventually resolved with continued infusion of fresh frozen plasma. Liver function tests indicated marked hepatocellular damage during the first three weeks of the illness. These abnormalities settled as the patient's metabolic state came under satisfactory control. CSF examination was performed on three occasions, the first being on the day of admission. The protein content varied between 0.25 g/l and 0.69 g/l, with white cell counts of 18/mm^3 lymphocytes on the first occasion reducing to 1 lymphocyte/mm^3. CSF and serological viral cultures and antibody titres were all negative. CSF with simultaneous serum electrophoresis showed an oligoclonal IgG banding pattern which was present on each examination, suggesting local synthesis. Serial EEGs remained dominated by diffuse slow wave activity unresponsive to spontaneous eye opening or hyperventilation.

During the next four weeks she suffered episodes of profound agitation during which she would moan and cry; on occasions she seemed to be more alert although never responsive. She continued to have frequent oculogyric crises and dystonic posturing. It was noted that in the neutral position her eyes were divergent and there was impaired convergence. Her breathing pattern was deranged, consisting of hyperventilation followed by prolonged apnoeic periods of up to 12 s; inspiratory and expiratory movements were broken in a characteristic 'ratchet' fashion. There was a persistent inappropriate tachycardia with frequent short bursts of supraventricular tachycardia and occasional premature ventricular ectopic beats. She remained unresponsive and rigid with some cogwheeling on passive movement,, the reflexes became asymmetrical and pathologically brisk with a right Babinski sign. Over the course of the following month she developed focal epilepsy, with twitching of the face and eye deviation; on two occasions the seizures became generalized. An EEG taken during one of the attacks showed, at the beginning of the twitching, prominent sharp wave activity and on one occasion long runs of sharp theta activity in the right hemisphere. An interictal EEG showed generalized high amplitude delta activity with some intermixed fast activity.

She returned to the hospital of referral after three months, still with day-night sleep reversal and occasional oculogyric crises. Her speech was monosyllabic, and she was poorly compliant and disruptive. The neurological signs were unchanged apart from the development of right-sided facial weakness. Formal psychometry showed her to be functioning at a mental age of approximately 3 years.

Case 2

A 63-year-old woman developed lumbar back pain, nausea and general malaise. Suddenly, two weeks later, she complained of double vision in all directions of gaze and blurring of vision. At this stage it was noted that she could not move her eyes easily or focus; megaphagia and a tendency to fall asleep during the day also occurred. She was admitted to hospital and was noted to have a visual acuity of 6/9 bilaterally, impaired colour vision, normal fundi and mild symmetric bilateral ptosis. She had absent pursuit and saccadic eye movements in the vertical plane and absent convergence. Horizontal eye movements and doll's head movements in the horizontal and vertical plane were normal. Optokinetic nystagmus was deranged to both right and left in the horizontal plane and absent in the vertical plane. She had diplopia on left lateral gaze.

Over the next few weeks she became increasingly drowsy and confused, and she suffered two episodes of nocturnal incontinence. She was disorientated and had marked blepharospasm, an immobile facies and a right palmomental reflex. Her breathing became progressively more irregular

P 25693

over the following two weeks; at times she was tachypnoeic with a respiratory rate of up to 60/min and on other occasions she experienced apnoea lasting up to 10 s. She was intubated, ventilated and a tracheostomy was performed. She then developed spontaneous intermittent hypertension and fluctuation of her body temperature between 37° C and 39.5° C.

Over the next two months she remained in an akinetic state and experienced at least twelve episodes during which her eyes became fixed in upgaze for about 30 min. She also had very frequent attacks of twitching of the mouth and facial muscles associated with blepharospasm and blepharoclonus. Second degree vertical nystagmus was noted and at times the eyes tonically deviated to the left. Reflex eye movements were full in all directions and the pupils were constricted to 2 mm bilaterally. Chvostek's sign was positive and she had brisk pout and bilateral grasp reflexes. There were no voluntary movements of the limbs. Cogwheel rigidity was present at both elbows and the reflexes were pathologically brisk in the arms with bilateral finger clonus. Abdominal reflexes were absent. The knee jerks were just present but the ankle jerks were absent and the right plantar response was extensor.

The EEG showed bilateral diffuse slow wave activity. Visual evoked responses were bilaterally abnormal, half-fields showing bilateral delay, worse on the right; cortical somatosensory evoked potentials were also delayed. Repeated lumbar punctures showed CSF protein levels between 0.3 and 0.58 g/l and white cell counts varying between 2 and 11 lymphocytes/mm^3. However, a lumbar puncture performed during the terminal stages of the illness showed 61 white cells/mm^3, predominantly histiocytes and ependymal cells. Electrophoresis showed an oligoclonal IgG pattern consistent with local synthesis within the CSF on all five lumbar punctures. Serological and CSF viral titres and cultures were negative.

During the last month of her life she remained in a vegetative state apart from occasional short interludes when she was more responsive and able to obey simple commands. Her breathing was erratic with episodes of rapid and shallow respiration. She finally died from a pseudomonal chest infection seven months after presentation.

A post-mortem examination was performed. This showed inflammatory changes throughout the whole of the cerebral hemispheres, subcortical regions and brainstem Perivascular lymphocytic infiltration involved the parahippocampal gyri, the caudate nucleus, putamen, globus pallidus, substantia innominata, hypothalamus, midbrain, pons and medulla. In the substantia nigra there was mild diffuse neuronal loss with degenerate neurons and extraneuronal pigment. Neurofibrillary tangles were not seen.

Case 3

A 23-year-old woman presented with a two-week history of increasing drowsiness. Shortly afterwards her eyes were noted to be moving strangely and she complained of blurring of vision and diplopia in all directions of gaze. She had mild frontal headaches and pain behind the eyes, particularly on movement, and developed clumsiness of her arms with a tendency to drop things. On examination she was obese with an expressionless face, drowsy and slow, but able to give a coherent account when awake. She was able to stand but her gait was unsteady and she tended to fall backwards. A rest tremor of her left hand was exacerbated when walking and she tended to stoop forwards with arms held in a dystonic flexed position. Her optic discs were pale and the pupils were medium sized with no reaction to light and only sluggish reaction to accommodation. There was bilateral ptosis, almost complete paralysis of eye movements to the left and right and severe limitation of vertical gaze. Doll's head eye movements were normal. There was marked neck rigidity and dystonic posturing of both hands; tone in all four limbs was increased with cogwheeling and marked rigidity on synkinesis. Power was normal but the reflexes were exaggerated with tonic spread and bilateral extensor plantar responses. Her breathing was regular but she was unable to hold her breath voluntarily.

Lumbar puncture yielded CSF with a protein of 0.36 g/l and 2 white cells/mm^3. CSF and serological viral titres and cultures were negative. The EEG showed moderate bilateral excessive theta activity. Visual evoked responses were of normal amplitude but the latencies were increased and half-field responses in the nasal field on the right were almost abolished. Caloric testing revealed the presence of bilateral internuclear ophthalmoplegia; simultaneous cold irrigation in both ears caused some downward movement but there was no upward deviation with bilateral, hot irrigation.

The patient became drowsy and the extrapyramidal features and ophthalmoplegia worsened; after six weeks, however, she became more alert, markedly aggressive and frankly deluded. At the time of discharge at three months, her behaviour was inappropriate, she was clinically depressed and extrapyramidal features were still present although less striking.

One year later the patient complained of headache, was severely depressed and had episodes of hyperventilation. On examination she had an expressionless facies, a wide-based gait and was slightly dysarthric and slow in response to commands although fully orientated. There was bilateral optic atrophy, impairment of pupillary reactions and continued impairment of upgaze. There was mild facial weakness, axial and limb rigidity and a mild tremor. The reflexes were symmetrical and brisk with bilateral Babinski signs and positive grasp reflexes. The visual evoked responses continued to show borderline delay and neuropsychological assessment suggested residual intellectual impairment.

Five years after the acute illness she remains in residential care, socially isolated because of aggression and functioning at an intellectually retarded level.

Case 4

A 31-year-old woman, who emigrated from Tanzania in 1970, presented with a three-day history of sore throat, malaise, severe neck pain and an inability to look downwards. On the day of admission she was found to be mumbling incoherently and behaving in a bizarre and disinhibited manner, rushing unsteadily and aimlessly around the ward. She then had two episodes of unconsciousness with pinpoint pupils, stertorous breathing, diminished gag reflex and no response to painful stimuli. On admission to The National Hospital three days later, she was pyrexial (38.5° C) and there was marked neck stiffness. She did not respond to commands or external stimuli but localized to painful stimuli, muttered incomprehensibly and covered herself when exposed. The eyes were divergent but moved in a conjugate manner. Her respiratory rate was 12/min with marked pauses during inspiration and expiration and she was therefore intubated and ventilated artificially. On the following day she had a tonic-clonic seizure. Over the next four days she was intermittently agitated and her level of consciousness fluctuated; at times she responded to her relatives but at others only to deep pain by flexion. She suffered occasional episodes of cataleptic posturing with her legs flexed and abducted, her arms flexed above her head and her eyes deviated upwards; these were thought to be oculogyric crises.

Serial lumbar punctures showed CSF protein levels varying from 0.48 g/l to 2.1 g/l and white cell counts varying from 7 to 44 lymphocytes/mm^3. Oligoclonal IgG banding was present in the CSF but not in the serum. CSF and serological viral titres and cultures were negative. The EEG showed diffuse unresponsive slow background activity.

Three months after presentation she continued to be restless with intermittent episodes of cataleptic posturing, responding inappropriately to external stimuli and muttering meaningless phrases.

DISCUSSION

Despite recent sporadic case reports of encephalitis lethargica in the literature, many physicians remain sceptical about its continued occurrence. In many of these the diagnosis has been based on the subsequent development of parkinsonian features following an acute, poorly documented encephalitis (Wohlfart *et al.*, 1961; Onuaguluchi, 1961; Duvoisin and Yahr, 1965; Williams *et al.*, 1979; Sacks, 1982; Clough *et al.*, 1983), or an encephalitic illness which differed in a number of ways from von Economo's classical descriptions (Leigh, 1946; Bickerstaff and Cloake, 1951; Barrett *et al.*, 1952; Espir and Spalding, 1956; Hunter and Jones, 1966; Poser *et al.*, 1969; Bojinov, 1971; Misra and Hay, 1971; Herishanu and Noah, 1973; Miyasaki and Fujita, 1977). Only Rail *et al.* (1981) can be said to have described the clinical features of an acute encephalitic illness resembling those described by von Economo and even in this series the accounts of the acute illness are often absent or incomplete.

Extrapyramidal syndromes may follow a number of different viral encephalitides but a causal relationship has not conclusively been established, nor can these conditions be considered identical to encephalitis lethargica (Burnell, 1922; Marinesco and Draganesco, 1928; Meyer, 1943; Dimsdale, 1946; Mulder *et al.*, 1951; Barrett *et al.*, 1952; Brewis, 1954; Walters, 1960; Richter and Shimojyo, 1961; Warembourg *et al.*, 1962; Thieffrey *et al.*, 1963; Eadie *et al.*, 1965; Bojinov, 1971; Marttila and Rinne, 1976; Fahn, 1977; Miyasaki and Fujita, 1977). Acute transient parkinsonian states have been seen during western equine encephalitis (Mulder *et al.*, 1951), coxsackie B (Walters, 1960; Poser *et al.*, 1969), measles (Meyer, 1943), Murray Valley (Burnell, 1922) and chicken pox encephalitis (Marinesco and Draganesco, 1928; Warembourg *et al.*, 1962; Thieffrey *et al.*, 1963). Japanese B encephalitis (Richter and Shimojyo, 1961; Goto, 1962) has been reported to be followed by parkinsonian sequelae but the postencephalitic syndrome differs from that following encephalitis lethargica in being more benign, without oculogyric crises and not showing a latent period. Molder *et al.* (1951) described two episodes of presumed oculogyric crises in a patient with parkinsonism following Western equine encephalitis.

The 4 patients described fulfil many of the criteria for the diagnosis of acute encephalitis lethargica. Cases 1 and 4 manifest features of the hyperkinetic form and Cases 2 and 3 the somnolent ophthalmoplegic form. Three patients presented with a nonspecific illness, headache and mild meningism. Cases 2 and 3 had hypersomnolence at presentation with day-night reversal. Cases 1 and 4 manifested an acute onset of general unrest and disturbed behaviour, to such an extent that an initial diagnosis of catatonic schizophrenia was made and the progression over the next week suggested the diagnosis of the neuroleptic malignant syndrome. Three of the patients were pyrexial within a few days of admission and Case 1 suffered a severe toxic disturbance with disseminated intravascular coagulation and hepatocellular abnormalities. Despite extensive investigations no underlying cause for this could be found. These systemic disturbances, commonly reported in von Economo's original cases, were ascribed to the toxic effects of the virus.

During the acute illness some patients develop catatonic psychotic states, hallucinations, akinetic mutism, hyperexcitability, obsessional behaviour, Korsakoff psychoses and klazomania (compulsive coprolalia) (Benedek, 1925; Wohlfart *et al.*, 1961). The importance of the mental sequelae of encephalitis lethargica was emphasized by Hunter and Jones (1966) who described 6 cases with a variety of psychiatric syndromes, hypomania, depression or anxiety. Disorders of mood with apathy, emotional dullness and loss of affective responsiveness have also been noted in survivors, as have permanent impairment of intellect and persistent psychotic behaviour. Psychiatric disturbances occurred in all the patients. Case 2 was confused and disorientated on admission but the hypersomnolence and akinetic mutism which were features of the remaining course of her illness made later assessment impossible. The other 3 patients showed severe prolonged psychiatric disturbances. The first patient presented a remarkable picture throughout her illness. Following an initial period of restlessness, uncooperativeness, emotional lability and mutism, she developed a bizarre form of compulsive behaviour, pseudomasturbation and klazomania. Over the ensuing weeks she remained in a state of akinetic mutism, occasionally appearing to recognize her mother but otherwise not responding to external stimuli. However, on a number of occasions she seemed to undergo episodes of profound agitation in which she would violently thrash around in the bed and seem to be more alert. Slowly, after four weeks, she became more responsive but behaved in an infantile and inappropriate manner, with violent outbursts. She had previously been an intelligent woman but by the time of her return to the referring hospital, psychological testing showed her to be functioning at a mental age of approximately 3 years. Case 3 became violent and attempted to bite members of the staff in the first six weeks of her admission. Although she had probably always functioned below the average range, there was residual intellectual impairment one year after admission. She was also noted to be clinically depressed, emotionally labile with tearful outbursts, and hypochondriacal. In Case 4 the illness presented with disinhibited behaviour and her intellect and behaviour remained seriously disturbed several months after resolution of the acute phase of the illness.

All the patients showed alterations in the state of consciousness. This varied from lethargy to coma. In Case 1 the sleep pattern was noted to be reversed during the initial stages of the disease. She then lapsed into stupor (Plum and Posner, 1983) for two months. Although her level of consciousness improved she has continued to show inversion of sleep pattern. In the initial stages Case 2 showed a tendency to fall asleep inappropriately during the day. She became increasingly somnolent, lapsing into coma and ultimately a persistent vegetative state before death.

All the patients showed signs compatible with basal ganglia damage: cogwheel rigidity, an expressionless mask-like facies and slowness and paucity of movement were present to varying degrees. There was a coarse rest tremor in 3 of the patients and chorea and dystonia were present in 2. Monosyllabic, hesitant speech was also a feature in 2 patients. The development of oculogyric crises and blepharospasm during the acute phase of the illness is characteristic (von Economo, 1931; Onuaguluchi, 1961; Clough *et al.*, 1983). Oculogyric crises may occur as an idiosyncratic reaction to certain drugs, especially metoclopramide and phenothiazines. However, if a drug cause can be excluded, and when associated with parkinsonism, oculogyric crises are considered to be pathognomonic of encephalitis lethargica, both during the acute encephalitic phase and as a feature of postencephalitic Parkinson's syndrome. Oculogyric crises occur in 30 to 60% of patients with postencephalitic parkinsonism but their frequency during the acute encephalitic illness is not known (Onuaguluchi, 1961; Clough *et al.*, 1983). This phenomenon was observed in 3 of the patients in whom it persisted throughout the course of the illness, although becoming somewhat less frequent with time.

The bulbar nuclei are also involved in the acute encephalitic illness. One patient showed facial weakness and another frequent cardiac arrhythmias. In Case 2 episodic hypertension was noted. The most striking brainstem feature, however, was the presence of respiratory abnormalities. Respiratory disorders of several kinds were described, including increased respiratory rate, apnoeic episodes, myoclonic jerking of the diaphragm, and staccato, ratchet and cluster breathing. Respiratory disturbances and cardiac arrhythmias are particularly serious and the most life-threatening feature of the acute illness. Respiratory abnormalities occurred in all the patients; sleep recordings of respiratory movements in Case 1 showed episodes of apnoea, ratchet and cluster breathing which resulted in hypoxic episodes without obvious upper airway obstruction. Case 2 suffered episodes of tachypnoea, respiratory irregularities and apnoea necessitating artificial ventilation. In Case 3 the respiratory pattern was regular but she was unable to hold her breath voluntarily, and in Case 4 inspiration and expiration were interrupted by irregular pauses. Megaphagia suggested hypothalamic involvement in Case 2 during the initial phase of the illness.

We propose that a number of clinical features may be considered as major criteria supporting the diagnosis of encephalitis lethargica. It should comprise an acute or subacute encephalitic illness which has as part of its clinical picture at least three of the following major criteria: (1) signs of basal ganglia involvement, (2) oculogyric crises, (3) ophthalmoplegia, (4) obsessive-compulsive behaviour, (5) akinetic mutism, (6) central respiratory irregularities, and (7) somnolence and/or sleep inversion.

The CSF is also frequently abnormal, particularly in those forms which manifest meningeal irritation. Some patients show a modest increase in pressure and protein content. In the early stages a mild/moderate pleocytosis may be present, the number of cells, predominantly lymphocytes, varying generally between 5 to 20/mm^3 but rarely as high as 500/mm^3. Lumbar puncture showed the CSF protein level to be elevated in 3 of the patients and 2 showed a mild to moderate increase in the lymphocyte count. The CSF glucose was normal in all cases. Williams and colleagues (1979) described 2 cases of progressive parkinsonism after an encephalitic illness in whom oligoclonal IgG bands were present in the CSF. There was no oligoclonal banding in 6 controls with idiopathic Parkinson's disease. Oligoclonal IgG bands may be observed in the CSF during acute viral infections such as herpes simplex encephalitis (Felgenhauer *et al.*, 1980; Vaheri *et al.*, 1982), mumps meningitis (Vandvike *et al.*, 1978), and chronic mumps encephalitis (Julkunen *et al.*, 1985). Oligoclonal IgG proteins may be detected in the CSF during the second week after the onset of mumps meningitis and as early as the sixth day after the onset of herpes simplex encephalitis and may persist for many months. It is unclear whether a continued presence of oligoclonal IgG in the CSF reflects an antibody response to an active infection or an activation of selective antibody-producing cells due to other factors. In this series, 3 patients had serial lumbar punctures performed during the course of the illness and in all of them CSF electrophoresis was performed with simultaneous serum electrophoresis. All the specimens of CSF showed oligoclonal IgG banding throughout the course of the illness. This includes the initial lumbar punctures which were performed between five and thirteen days after the first symptoms. These findings are the first report indicating local IgG synthesis within the CSF in the acute phase of clinically definite encephalitis lethargica and add support to the view that the condition is caused by a viral infection.

The EEG findings during the acute phase of the illness have only rarely been reported; they seem to reflect a diffuse encephalitic illness. There may be diffuse unilateral or bilateral slowing in the delta or theta frequencies but more focal sharp wave activity is seen in some cases. In the present study all 4 patients had diffuse slow wave activity with no definite lateralizing features. However, in Case 1 an EEG performed during an epileptic seizure showed occasional long runs of sharp theta activity in the right hemisphere before the tracing became obscured by movement artefact.

Abnormalities of evoked potentials have not previously been reported in encephalitis lethargica. The abnormal visual evoked potentials in Cases 2 and 3, despite reasonable fixation on the target, and delayed cortical component somatosensory evoked potentials in Case 3 suggested the presence of cortical involvement, as did the development of focal epilepsy in the same patient. These findings add support to von Economo's suggestion that diffuse cortical involvement is a feature of encephalitis lethargica.

The pathological findings of von Economo suggest there are nonpurulent, nonhaemorrhagic alterations limited to the grey matter, with preferential localization to the midbrain. Perivascular infiltration with engorged blood vessels and nerve cell necrosis are evident. Although the changes are most severe in the brainstem and basal ganglia, there was also involvement of the cerebral cortex and spinal cord. These findings, characterizing the acute cases, are replaced by more extensive tissue damage in the postencephalitic state. The neurofibrillary tangle was first described by Hallervorden in 1935 and the presence of this cytoplasmic inclusion in the substantia nigra has come to be regarded as one of the hallmarks of postencephalitic Parkinson's disease. Typically the tangles are found in connection with severe diffuse nerve cell loss. The histological findings in Case 2 are compatible with the early descriptions of the pathological findings in acute encephalitis lethargica.

In 1971 Bojinov stated that no author in the preceding forty years had observed the typical clinical features of encephalitis lethargica. This view was reinforced by Herishanu and Noah (1973) who commented that the majority of neurologists thought that von Economo's disease was a condition of the past. Poser *et al.* (1969) have suggested that paraencephalitic parkinsonism may not be a distinct syndrome but merely follow a number of different, nonspecific viral encephalitides. They have suggested that all parkinsonism, including the idiopathic and arteriosclerotic types, are essentially viral in origin and that the damage to the cells of the basal ganglia is the result of a viral meningoencephalitis, the parkinsonism becoming manifest later as a result of a secondary noxious insult. However, the clinical picture described by von Economo and manifested by a number of patients in the literature is sufficiently characteristic to allow a clinical diagnosis and to suggest a unifying aetiology.

We agree that a number of case reports of supposed encephalitis lethargica remain open to considerable doubt. Bickerstaff and Cloake (1951) described 3 cases of mesencephalitis and rhombencephalitis. The authors thought the cases unlikely to be encephalitis lethargica because of the gradual onset, minimal systemic disturbance, absence of reversal of sleep or disturbances of respiratory rhythm, the presence of complete bulbar palsies and the transitory nature of the parkinsonism in one patient. They considered a possible relationship to poliovirus. Hunter and Jones (1966) described 6 cases of possible encephalitis lethargica with psychiatric and ocular abnormalities. However, they make little mention of any extrapyramidal or pyramidal features and as the cases are not discussed individually, it is difficult to be sure on what grounds the diagnosis of 'mild or attenuated' encephalitis lethargica was made. Poser *et al.* (1969) described a case of a severe transient parkinsonian syndrome following a meningoencephalitis associated with the coxsackie virus type B2 in a 16-year-old boy. Fifteen months later the patient returned completely to his premorbid state. Apart from the development of an extrapyramidal syndrome he showed few of the features previously described as 'major diagnostic criteria', namely somnolence, ophthalmoplegia and oculogyric crises. Bojinov (1971) described 11 patients with encephalitis and an acute parkinsonian syndrome. Although these cases showed extrapyramidal and pyramidal disorders, ophthalmoplegia and sleep disorders, the authors preferred to call the condition a polioencephalitis of viral origin. Pathological examination of the brains of the fatal cases revealed a severe inflammatory necrosis of the substantia nigra with proliferation of phagocytic cells and abundant plasma cells and lymphocytes. A number of gliomesenchymal nodules and areas of perivascular round cell infiltration were found in the inferior olive, the dentate nucleus, the cerebellar cortex, the basal nuclei and the thalamus. The cerebral cortex, striate body and spinal cord were spared.

Misra and Hay (1971) described 3 patients who developed symptoms of acute schizophrenia. There were no abnormal neurological signs on presentation, but all the patients later showed clinical evidence of encephalitis. One developed a postencephalitic parkinsonian disorder and a second remained in a chronic schizophrenic state. However, the clinical details of the encephalitic illness are insufficient to sustain a diagnosis of acute encephalitis lethargica. Crow (1983) has cited the psychiatric abnormalities that occur in encephalitis lethargica as supportive evidence for the theory that schizophrenia could be due to a virus which is transmitted predominantly from schizophrenic patients to genetically predisposed individuals. Recently Carne *et al.* (1985) have reported 3 patients who suffered an acute encephalopathy associated with the appearance of antibodies to human T-lymphotropic virus (HTLV-III, HIV). These patients suffered mood changes and epileptiform seizures during the course of the illness but the neurological symptoms and signs resolved in all of them, and no residual CNS sequelae were noted.

Miyasaki and Fujita (1977) described a case of parkinsonism following a mild encephalitis of unknown aetiology, clinically distinct from von Economo's encephalitis. A post-mortem examination was performed five years after the acute encephalitis and showed that the neurons in the substantia nigra were extensively degenerated and presented Alzheimer's neurofibrillary tangles. Perivascular cuffing was observed in the frontal, parietal and temporal lobes, hippocampus and thalamus, as well as the substantia nigra. Rail *et al.* (1981) presented 8 patients who were believed to conform to the clinical features of encephalitis lethargica as defined within the paper. The encephalitic illness was reviewed retrospectively and in a number of cases the acute encephalitic illness was either poorly documented or not clearly distinguished from the postencephalitic sequelae, indeed 2 of the cases did not have a clear encephalitic illness. Most showed extrapyramidal abnormalities during the acute phase and all developed such features ultimately. Two patients showed florid positive motor symptoms and 3 suffered psychiatric manifestations. Other important features seen in some of the patients included focal motor abnormalities, oculogyric crises (3 cases), pupillary changes or gaze palsies (2 cases) and respiratory abnormalities (2 cases). The authors described the pathological appearances in 2 of their cases of postencephalitic Parkinson's disease. There was severe neuronal loss in the substantia nigra and locus coeruleus. The remaining neurons showed prominent neurofibrillary tangles but no Lewy bodies or Alzheimer's plaques were found. Neurofibrillary tangles were also seen in the dentate nucleus, corpus striatum and cortical neurons in 1 patient. Rail and colleagues defined 9 clinical features of encephalitis lethargica and our experience concurs that these are amongst the most important criteria for establishing the diagnosis. Certainly in the presence of an acute encephalitic illness, the development of extrapyramidal signs, oculogyric crises (provided there is no relevant drug history), behavioural disturbances, ocular, respiratory and sleep abnormalities are the main characteristic features. Evidence of pyramidal or diffuse cortical involvement during the acute encephalitic illness is common but cannot be considered diagnostic. We do not accept that the previous administration of neuroleptics should exclude the diagnosis although it is important to recognize that acute dystonic reactions and the neuroleptic malignant syndrome may superficially mimic the disorder.

Herpes simplex encephalitis may resemble encephalitis lethargica with focal motor signs, isolated cranial nerve palsies, behavioural disturbances, amnesia and confusional states preceding coma (Drachman and Adams, 1962). However, extrapyramidal features, oculogyric crises, sleep inversion, ophthalmoplegia and respiratory disturbances are rarely, if ever, seen during the course of herpes simplex encephalitis and necrotic damage of the temporal and frontal lobes is not a feature of encephalitis lethargica.

Multiple sclerosis (MS) may also present with a leucoencephalitic picture of drowsiness, stupor and cranial nerve palsies which may be clinically indistinguishable from focal brainstem encephalitis. Patients with acute 'leucoencephalitic' MS do not suffer oculogyric crises and extrapyramidal features, and mental disturbances are extremely unusual. Although psychiatric disturbances are common in MS, presentation with schizophrenic psychosis has only rarely been reported (Parker, 1956; Geocaris, 1957).

Elizan and her colleagues (1980) found an increased frequency of HLA B14 (44%) in postencephalitic parkinsonism compared with matched controls. However, Lees *et al.* (1982) failed to show any difference in phenotypic frequencies of HLA types in 21 patients with parkinsonism secondary to von Economo's encephalitis compared with a large group of controls. These findings failed to support the hypothesis of genetic susceptibility to postencephalitic parkinsonism. A possible explanation for the findings of Elizan *et al.* was that all the patients they described shared a common East European Jewish origin. Marttila *et al.* (1977) failed to find increased serum titres to four strains of influenza A in 20 patients with postencephalitic parkinsonism and Elizan *et al.* (1978) found similar results in 27 patients. A later study of Elizan *et al.* (1979) failed to show increased CSF or serum titres for haemagglutination inhibition antibodies to arborvirus. They did, however, show lowering of titres of herpes simplex virus type 2 in postencephalitic patients compared with controls but it is unlikely that this virus could be causally associated with the disease.

We have been unable to demonstrate any significantly elevated or rising viral titres in blood or CSF in our patients. It is possible that encephalitis lethargica may be a specific response to a variety of viral infections or a rare illness due to a specific neurotropic virus which stimulates a B cell immunoglobulin response within the CSF. These cases, however, re-emphasize that sporadic cases identical to those reported by von Economo in the 1917–1928 pandemic continue to occur and may be responsible for cases of Parkinson's syndrome in the community. The delayed appearance of Parkinson's syndrome following a seemingly full recovery from the acute encephalitic illness may be due to a continuing virally-mediated nigral damage or alternatively to decompensation as a result of ageing effects in an already compromised substantia nigra.

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PARKINSON'S DISEASE

COGNITIVE CHANGES IN RELATION TO TREATMENT RESPONSE

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SUMMARY

Four groups of patients with Parkinson's disease matched for age, education and IQ were categorized by response to treatment and compared with a normal control group. The patient groups were (1) No Treatment (de novo); (2) Good Response (including minor fluctuations in symptoms); (3) Fluctuations (significant, including 'on-off' phenomena) and/or marked Abnormal Involuntary Movements (dyskinesias); and (4) Poor Response ('secondary treatment failure' characterized by significant deterioration over time in all major symptoms). As a previous investigation had established that neuropsychological tests thought to be sensitive to the functional integrity of the frontal lobes are selectively impaired in Parkinson's disease, the first phase of this study compared the five groups on five such tests and two tests of psychomotor ability. While all patient groups displayed deficits on the psychomotor tests and on several tests associated with frontal lobe function compared with normals, only the Poor Response group was impaired on all tasks. In a second phase, comprehensive testing of additional cognitive processes such as attention, mnemonic, and visuospatial functions, the latter two traditionally thought to depend primarily on posterior cortical regions, revealed no significant cognitive deficits in any patient group. Results are discussed with respect to the involvement of the nigrostriatal and mesocortical dopaminergic systems.

INTRODUCTION

Idiopathic Parkinson's disease (PD) is heterogeneous in many respects. While there is agreement on the classical and characteristic triad of motor symptoms which herald this disorder, progression with respect to tremor, rigidity and bradykinesia varies considerably amongst individuals as does the evolution of additional motor symptoms (Lieberman, 1974). Mental changes may also range from a small cluster of deficits (Taylor *et al.*, 1986*a*) to global dementia (Taylor *et al.*, 1985). Furthermore, response to levodopa and/or dopamine agonists is difficult to predict as, in any group of patients, it varies from near resolution of symptoms to the appearance of secondary motor and mental complications, to no observable benefit (Marsden and Fahn, 1982).

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Disease severity has been identified as a factor predictive of cognitive dysfunction in PD. Mortimer and his colleagues (1982) measured symptom severity and found that bradykinesia was correlated with performance on visuospatial tasks. However, the strength of the association was not impressive, leading those authors to speculate that many other factors could contribute to patient scores. Indeed, a simple relationship between motor severity and mental status is questionable when one considers that many patients can fluctuate between extremes of physical disability while preserving a constant level of mental function (Brown *et al.*, 1984). Alternatively, it is possible that separate groups of PD patients can be identified in terms of response to treatment and that this factor is important in predicting the extent and degree of cognitive involvement. The issue is of critical importance if failure to benefit from antiparkinsonian agents is associated with significant mental changes.

Several studies have suggested that dementia may be associated with a poor response to treatment and neuropathological changes in the cerebral hemispheres outside the basal ganglia. In a pathological study Lieberman *et al.* (1979) identified two groups of PD patients. The larger group (70%) was characterized by normal age-related cortical changes, typical features of PD, improvement under levodopa, and intact mentation. A smaller number (30%) in whom cortical changes were compatible with Alzheimer's disease, had a history of dementia, later onset of PD, and a less favourable treatment response. In a cross-sectional study of living patients, Sroka *et al.* (1981) found no significant evidence of cortical atrophy or ventricular enlargement as visualized by CT scanning in most patients with typical features of PD. Conversely, in patients with an atypical disease presentation, ventricular enlargement and permanent cognitive deficits were strongly associated. In a recent longitudinal study, ventricular enlargement was also correlated with cognitive decline (Portin *et al.*, 1984). In this case poor response to treatment was later identified as a strong predictor of the observed progressive mental changes (R. Portin and U. K. Rinne, 1985 personal communication). Unfortunately, 60% of the patients studied had previously undergone single or multiple thalamotomies for relief of symptoms.

The present authors, engaged in an ongoing investigation of PD, have been impressed with a number of patient attributes which interact with cognitive processes. In an extensive study of intellectual, memory, visuospatial and executive functions, deficits in a group of 40 nondemented idiopathic PD patients were restricted to a small cluster of abilities thought to depend upon the integrity of the premotor and prefrontal regions (Taylor *et al.*, 1986*a*). Importantly, these regions are the cortical targets of basal ganglia outflow within the cortico-caudato-nigro-thalamo-cortical 'complex' loop and the cortico-putamino-pallido-thalamo-cortical 'motor' loop (DeLong *et al.*, 1983). Within the cluster of cognitive processes affected by PD, interactions between selective tasks and disease severity, age, intelligence and laterality of symptoms were noted. However, as only 10% of the patients in that study had lost all initial treatment benefit, exploration of the relationship between this variable and observed deficits required further investigation.

To examine this issue four groups of patients were selected and identified on the basis of response to treatment. Assignment was predicated upon extensive experience with levodopa and dopamine agonists which, over the last decade, has revealed a number of complications associated with these therapies (Agid *et al.*, 1979; Shaw *et al.*, 1980; Weiner, 1982; Lang *et al.*, 1983; Yahr, 1984). It is now apparent that approximately 60% of levodopa-treated patients lose between 30-40% of initial improvement within three to four years. Despite this outcome only a small number fail to maintain any benefit in the cardinal motor symptoms comparable to initial medication response. This 'poor response' group typically obtains a moderate-to-good initial response which gradually and insidiously deteriorates over time, eventually leading to no apparent benefit at all. Nevertheless, most such patients remain responsive to levodopa, confirmed by the obvious increase in symptoms which accompanies drug withdrawal. Marsden and Fahn (1982) have labelled this phenomenon 'secondary treatment failure' to distinguish such patients from 'primary treatment failures' where no favourable response to medication occurs at any point in the treatment history.

'Positive' complications can also accompany levodopa treatment. A number of patients suffer marked fluctuations in symptom state predictable from medication schedules where, for example, 'wearing off' of the beneficial effects of one dose occurs before the next dosage is due (Fahn, 1982). Less commonly, unpredictable variations emerge which range from marked akinesia to periods of good mobility (on-off). Additionally, many patients on levodopa treatment for more than five years develop some form of abnormal involuntary movements (AIMs). Disabling dyskinesias most frequently accompany the more marked drug-induced fluctuations (Weiner, 1982).

These limiting factors in levodopa management have led to the use of dopamine agonists as an alternative or conjoint form of therapy. However, dopamine agonists often increase the risk of yet another complication associated with the treatment of PD patients, the induction of medication-linked psychiatric symptoms and/or confusional states. This problem is particularly evident in patients who have suffered such side-effects during earlier levodopa administration (Lang *et al.*, 1983).

Nevertheless, the current study hypothesized that nondemented PD patients without thalamotomy who suffer secondary treatment failure while remaining typical with respect to the signs and symptoms of the disease, will be differentiable cognitively from normal control subjects and patients who either do not yet require treatment, or who continue to receive observable benefit even if this is fraught with obvious drug-related 'positive' motor complications. In addition, cognitive functions at risk in secondary response failure should include those observed to be impaired in PD patients in the earlier study (Taylor *et al.*, 1986*a*). In that sample, deficits were confined to mental operations which are 'executive' in nature and thought to depend upon frontal lobe-based cognitive subroutines. In such executive tasks, the processing of information requires task-specific organization of a plan or strategy for successful performance. Additional tests, which were explicit in their instructions and easy to monitor, or which depended upon retrieving familiar or well-organized information, were not impaired although they too are considered 'executive' and implicate the frontal lobes.

Accordingly, in the first phase of the present study, a subgroup of executive tasks was administered to five carefully matched groups. Four were composed of PD patients classified according to treatment response. The fifth was a group of normal control subjects. We sought to determine whether or not 'secondary treatment failure' is similar to other PD groups in displaying deficits restricted to executive tasks requiring the subjective organization of task-specific strategies (Phase 1). Subsequently, analyses of intellectual functions, memory, visuospatial processes, attention span, and sustained concentration were undertaken in all five groups to gauge both intergroup PD differences which could influence more purely cognitive operations in a nonspecific manner and to define the range of possible subgroup differences (Phase 2). Data were extracted from a comprehensive neuropsychological battery routinely administered to all patients and control subjects (Taylor *et al.*, 1986*a*). If failure to maintain an obvious clinical response to levodopa is predictive of evolving cognitive dysfunction as well as declining motor status, then patients with secondary treatment failure should exhibit a profile of cognitive deficits differentiable from, and/or more extensive than, all other groups.

SUBJECTS

Four groups of nondemented idiopathic PD patients, independently diagnosed by two neurologists, and one normal control group were selected for this study. Patients with additional neurological manifestations such as cerebellar disturbances and disproportionate oculomotor or autonomic dysfunction were excluded, as were those with a premorbid history of significant emotional disturbance, or signs of drug toxicity at the time of testing. Patients with clinical signs of depressive affect subsequent to the onset of PD were not excluded since we had previously determined that this variable had no effect on cognitive performance (Taylor *et al.*, 1986*b*). All patients were rated on a modified Columbia scale (Duvoisin, 1971) which measures disease severity (tremor, rigidity and bradykinesia), and the Northwestern University scale (Canter *et al.*, 1961) which measures disability (expressed in the activities of daily living) during their initial visit to the Movement Disorders Unit at Toronto Western Hospital, and at regular intervals during follow-up. The five groups were matched according to age, educational status, and premorbid intellectual level. The last was estimated with the National Adult Reading Test (NART), determined to be a stable and reliable estimate of original function (Nelson and O'Connell, 1978).

The careful matching procedures considered necessary in view of the impact of both intellectual factors and age on cognitive functions of interest, limited group size to 9 subjects each, as PD patients also had to meet designated treatment group criteria. This sample size, while relatively small, considering a pool of 150 neuropsychologically and neurologically assessed patients from which to draw, is entirely appropriate and in accordance with the requirements of analysis of variance procedures where, as in the present experiments, subjects are carefully selected to represent fairly the populations under consideration and the theoretical assumptions underlying these techniques are met (Ferguson, 1971).

All subjects gave informed consent.

Group NT

No treatment. All patients in this group were recently diagnosed and sufficiently able to remain untreated at the time of this study.

Group GR

Good response to treatment. Patients in this group were receiving levodopa in combination with a peripheral decarboxylase inhibitor, a dopamine agonist alone, or a combination of these two agents. Treatment was predicated upon the most favourable regime for any individual. While a number of patients in this group experienced minor fluctuations or AIMs in the course of a day, these symptoms did not disrupt activities of daily living.

Group FA

Fluctuations and AIMs. Patients in this group suffered major medication-related fluctuations which, in most patients, were accompanied by involuntary movements. Assignment to this group was determined by the severity of these complications which frequently brought ongoing activities to a halt. Dyskinesias and/or fluctuations were predictable in 7/9 patients on the basis of medication-delivery. The 2 remaining patients were classified as 'on-off' because of frequent rapid, striking and unpredictable alterations in motor status. The majority of patients in this group were on a combined pharmacological regime (levodopa plus bromocriptine or pergolide) in an effort to reduce treatment-related problems. Neuropsychological testing was confined to periods of maximum treatment benefit.

Group PR

Poor response to treatment. All patients in this group had a moderate-to-good initial treatment response. At the time of testing they exhibited generalized symptomatic decline and were strikingly disabled compared with their initial response despite manipulation of levodopa alone or in combination with other antiparkinsonian agents. While 2 patients experienced fluctuations, their status during periods of maximal benefit remained well below initial response levels. Despite poor response to treatment, all patients in this group remained typical with respect to the classical symptoms of PD.

Group NC

Normal control group. All individuals in this group were volunteers with no history of psychiatric or neurological disorder.

As stated, exclusion criteria for the PD patients comprised evidence of dementia, significant emotional disturbance before the onset of PD, medication-induced confusion and/or hallucinosis at the time of neuropsychological testing, or end stage disease. The presence of dementia was determined by clinical and neuropsychological criteria employed in an investigation of the frequency of this symptom in a sample of 100 consecutive PD patients (Taylor *et al.*, 1985). Bed-ridden patients in Stage V (Hoehn and Yahr, 1967) were excluded as they were too severely disabled to undergo valid neuropsychological testing.

Age, education and premorbid IQ estimated with the NART, were carefully matched in the five groups as seen in Table 1. Duration of disease, duration of treatment and disease stage (Hoehn and Yahr, 1967) are also presented in Table 1 for the four PD groups, as well as laterality of symptoms for patients in Groups NT and GR. In addition, the score on the Purdue Pegboard (Lezak, 1983), a measure of speed of single and combined hand movements in placing pegs in a board, is presented as an index of bradykinesia for the four PD groups and the normal control group. In a previous investigation (Taylor *et al.*, 1986*a*), this test was strongly correlated with the clinical evaluation of symptom severity.

TABLE 1 MEAN VALUES (WITH SD) FOR AGE, EDUCATION, IQ, DURATION OF DISEASE AND TREATMENT, SEVERITY SCORES, AND DISEASE STAGE AND LATERALITY FOR THE 5 GROUPS

*Group**	*Age (yrs)*	*Duration of disease*	*Duration of treatment*	*NART IQ*	*Education*	*Purdue*
NT	61.1 (6.2)	2.1 (1.3)	—	113.8 (6.0)	13 (3.6)	32.5 (5.8)
GR	62.0 (5.2)	9.3 (4.1)	6.2 (4.4)	114.5 (7.7)	14 (4.0)	36.5 (8.1)
FA	61.1 (5.4)	13.8 (4.4)	10.8 (3.6)	114.8 (8.6)	13 (4.3)	29.8 (10.3)
PR	61.2 (8.4)	8.0 (4.1)	7.5 (3.9)	114.7 (9.4)	13 (3.3)	24.3 (6.0)
NC	62.4 (7.7)	—	—	113.7 (10.0)	14 (3.6)	47.3 (5.9)

	Stage					*Laterality***		
	I	*II*	*III*	*IV*	*V*	*R*	*L*	*B*
NT	7	2	—	—	—	5	4	—
GR	1	5	3	—	—	6	2	1
FA	—	1	8	—	2 (when off)	—	—	9
PR	—	1	7	1	—	—	—	9
NC	—	—	—	—	—	—	—	—

* 9 patients/group throughout. ** Laterality of motor symptoms at time of testing. NT = no treatment. GR = good response to treatment FA = fluctuations and AIMs. PR = poor response to treatment. NC = normal control group.

METHODS

Phase 1

Tests of executive functions, previously identified as sensitive to the functional integrity of the frontal lobes, were analysed for all five groups. These included four tests, described below (1-4), which had discriminated between PD patients and normal subjects (Taylor *et al.*, 1986*a*), and an additional two tasks (5, 6, described below) to explore more fully any intergroup differences.

1. *The Wisconsin Card Sorting Test* (*WCST*) (*Milner, 1964*). In this test 128 cards with stimuli in various combinations of colour, form and number, must be sorted according to an unknown and varying sequence of correct principles using only error feedback. The score is the number of correct categories identified. Both the generation and shifting of mental strategies are required.

2. *Delayed Recognition Test* (*DRT*) (*adapted from Albert and Moss, 1984*). In this task sets of 14 words or 14 randomly arranged circles are displayed on a video screen in increasing set size from 1-14 for 15 s per exposure followed by a 10 s delay. The word list, which contains highly familiar five-letter words, is presented in a variable array each time it appears. The pattern of circles always maintains a fixed position for each item on each presentation of the increasing matrix. The task in both cases is to identify the new stimulus added in following each delay (nonmatch to sample). The score is the sum of items correctly recognized before the first error. In previous testing, PD patients displayed a deficit on the spatial list alone (Taylor *et al.*, 1986*a*).

3. *Rey Auditory Verbal Learning Test* (*RAVLT*) (*Lezak, 1983*). This test presents 15 words for immediate free (uncued) recall over 5 trials. The score is the total number of words recalled. The 15 words are then presented embedded in a paragraph with 15 distractors. The score on the recognition phase is the total correctly identified minus errors. The free recall portion of this test is a measure of information acquisition (learning) as the stimulus list exceeds normal retention span on all but the later trials, particularly in the older population. Successful performance, therefore, depends on the ability to organize subjectively the unrelated stimuli into meaningful units (Sternberg and Tulving, 1977).

4. *Bead-Tapper* (*BTap*) (*Talland and Schwab, 1964*). In the first phase of this test, 48 beads of 3 different shapes are sorted according to shape for 1 min with the preferred hand. Following this a telegraph key is depressed as quickly as possible with the index finger of the nonpreferred hand. In the final phase, both these activities are performed simultaneously for 1 min. The score is the 'savings' on the tapping component (single tapping score/combined tapping score) where each individual serves as his own control with respect to tapping speed. Talland and Schwab (1964) hypothesized that the motor planning required for the combined task was central in origin rather than a function of the effector system.

5. *Verbal Fluency Test* (*VF*) (*Benton, 1968*). This test measures the ability to generate words spontaneously (within specified constraints), to designated letter categories as quickly as possible in 1 min.

7. *Trail Making Test* (*TMT*) (*Halstead, 1947*). In the first phase (A), the numbers 1-25, distributed pseudorandomly on a sheet of paper, must be connected in order by a continuous pencil line as quickly as possible. The time required serves as a baseline for motor speed for comparison with phase B where the numbers 1-13 and letters A-L, again distributed pseudorandomly, must be connected in an ordered alternating number-letter sequence as quickly as possible. The score is the difference in time (B-A) to completion for the two phases. This test measures efficiency of mental set alternation having controlled for the motor requirement.

Each of these tasks was presented to all five groups in a fixed sequence within the larger test battery. The results of all but the RAVLT recognition memory phase (phase 2) and the DRT test were subjected to analysis of variance according to group (Statistical Analysis Systems, 1982). The latter two tests were analysed using the Kruskal-Wallis analysis of variance for nonparametric data (Ferguson, 1971).

Phase 2

The second group of results included tests of attention and sustained concentration to assess the possible contribution of these variables to intergroup effects. Attention was measured by raw scores on the Digit Span Test (Wechsler, 1981), while sustained concentration was judged by performance on the DRT word list, a simpler delayed nonmatch-to-sample task which previously failed to distinguish PD patients from normal controls (Taylor *et al.*, 1986*a*). Moreover, additional testing of cognitive functions was considered necessary to examine the extent of any intergroup differences outside the domain of frontal lobe functions. Accordingly, the entire Verbal section of the Wechsler Adult Intelligence Test—Revised (Wechsler, 1981) was included to assess current level of intellectual function. The Performance section was omitted as both motor demands and time constraints render it inappropriate for individuals who suffer movement disorders. Free recall was examined with the Logical Passages (LP), Visual Reproduction (VR), and Paired Associate Learning Test (PALT), of the Wechsler Memory Scale (WMS) (Wechsler and Stone, 1945), administered on both an immediate and 30 min delayed basis. All WMS comparisons employed raw score values. Recognition memory was assessed on the second phase of the Rey Auditory Verbal Learning Test (RAVLT). Finally, visuospatial processing was examined with tests of numerical reasoning in space (Block Test; Terman and Merill, 1973), mental rotation in matching similar geometric visual patterns (Item 99; Luria Nebraska battery, Golden *et al.*, 1980), and egocentric orientation (identifying right and left turns on an imaginary route walk (Map Test; slightly shortened from Money, 1976)). With the exception of the Map Test, RAVLT, and the Delayed Recognition Tests (DRT), all items were drawn from standard psychological batteries in widespread clinical use. Results of WAIS-R verbal IQ, and WMS tests were submitted to an analysis of variance. RAVLT recognition, the DRT word list, and the visuospatial tests were analysed nonparametrically with the Kruskal-Wallis test because of ceiling effects and nonnormal distributions of data. Tests, abbreviations, and functions are summarized in Table 2.

TABLE 2 TESTS AND FUNCTIONS INVESTIGATED

	Phase 1
1. Wisconsin Card Sorting (WCST)	Set formation, maintenance and shifting
2. Delayed Recognition Test (DRT), spatial	Recognition span for spatial position
3. Rey Auditory Verbal Learning Test (RAVLT)	Free recall in supraspan word list learning
4. Bead-Tapper (B-T)	Multiple manual set performance
5. Verbal Fluency (VF)	Speeded access of semantic information
6. Trail-Making (TMT)	Alternation of mental set
	Phase 2
Digit Span	Immediate attention span
Delayed Recognition Test: words (DRT)	Sustained attention in word list recognition
Wechsler Verbal IQ	Current intellectual level
Logical Passages (LP)	Immediate and delayed recall of prose
Visual Reproduction (VR)	Immediate and delayed recall of images
Paired Associate Learning Test (PALT)	Immediate and delayed recall of word associations
Rey Auditory Learning Test (RAVLT)	Recognition memory for word list
Block Test	Numerical reasoning in space
Item 99	Mental rotation
Map Test	Right-left orientation

RESULTS

As seen in Table 1, duration of disease varied widely in the PD groups with an expected brief period in Group NT. Group PR had a shorter disease duration than Groups GR and FA. In relative terms, the ratio of duration of treatment : duration of disease was smallest in Group PR. Severity scores (represented by the Purdue test) revealed significant differences between all PD groups and normal controls, as expected.

The means and SD of the scores obtained by the five groups on the six executive tests are presented in Table 3 in conjunction with results of the analyses of variance

TABLE 3 MEANS AND SD (IN PARENTHESIS) FOR THE 5 GROUPS ON THE 6 TESTS SENSITIVE TO FRONTAL LOBE FUNCTION

Group	*RAVLT*	*WCST*	*VF*	*TMT*	*B-Tap.*	*DRT** (*spatial*)
	F = 11.06 $P < 0.0001$	F = 3.6 $P < 0.02$	F = 2.96 $P < 0.04$	F = 7.3 $P < 0.0002$	F = 14.67 $P < 0.0001$	$\chi^2 = 17.81$ $P < 0.002$
NT	41.3 (8.9)	4.0 (3.1)	44.0 (11.2)	64.5 (40.0)	45.5 (20.4)	12.5 (2.1)
GR	41.2 (6.7)	3.2 (2.2)	39.7 (12.2)	40.3 (14.6)	62.4 (9.2)	10.5 (2.6)
FA	40.8 (6.7)	3.7 (3.1)	43.1 (13.0)	56.0 (20.9)	49.6 (12.1)	10.0 (3.6)
PR	29.6 (5.5)	2.0 (2.1)	28.1 (5.1)	164.1 (112.6)	23.5 (18.2)	6.4 (3.1)
NC	51.6 (6.6)	6.7 (1.9)	41.2 (12.5)	52.6 (23.6)	76.0 (13.6)	12.7 (1.2)

* Analysed nonparametrically. RAVLT = Rey Auditory Verbal Learning Test. VF = Verbal Fluency. B-Tap = Bead-Tapper. WCST = Wisconsin Card Sort. TMT = Trail-Making Test. DRT (spatial) = Delayed Recognition, spatial set. For Group abbreviations, *see* Table 1.

by groups expressed in F ratios with associated levels of significance where parametric testing was appropriate. As ceiling effects were present in the DRT, analysis was conducted by the Kruskal-Wallis nonparametric analysis of variance test.

There were significant differences in the overall performance of the five groups on all six tests. For clarity of comparison, performance of the four PD groups on tests analysed parametrically are illustrated in bar graph format (fig. 1). As standard testing of homogeneity of variance was consistent with the principle that the PD samples were from the same population as the NC group (with the exception of Group PR on VF and TMT), the distance of each PD group mean from the mean of the normal control group is illustrated in terms of the SD for Group NC. Results of multiple range t tests are illustrated graphically. Test results in fig. 1 are separated into primarily motor (Purdue and Bead-tapper) and cognitive (WCST, RAVLT, VF, TMT) functions.

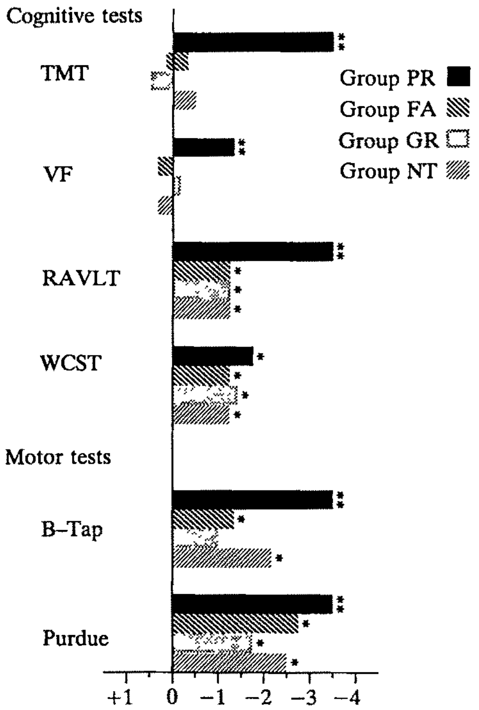

FIG. 1 Distance of mean group score in the four PD groups from mean NC group score (0) expressed in SD of NC performance. * Significantly different from NC ($P = < 0.05$); ** Significantly different from all other groups ($P = < 0.05$). TMT = Trail-Making Test, VF = Verbal Fluency; RAVLT = Rey Auditory Verbal Learning Test; WCST = Wisconsin Card Sorting; B-Tap = Bead-Tapper.

Fig. 1 reveals similarities and differences between Groups NT, GR and FA and the normal control subjects. These PD groups displayed deficits on RAVLT, WCST, BTap and Purdue. No differences were observed on VF or TMT. Although both Groups GR and FA performed the DRT spatial list more poorly than the NC group (Table 3), only Group GR reached significance (< 0.05) on later Mann-Whitney comparisons. Group FA approached significance (< 0.06).

In contrast, Group PR was impaired on all tests and, with the exception of WCST, performed the remaining five significantly more poorly than all other PD groups. Mann-Whitney tests also revealed lowered performance on the DRT spatial list compared with all other groups.

The consistent failure of Group PR to maintain comparable levels of performance with respect to the other PD groups prompted additional analyses of cognitive functions to assess (1) the possible contribution of deficits in attention and concentration, and (2) the extent to which cognitive operations, beyond those sensitive to the frontal lobes, might be affected. Results for Phase 2 are presented in Table 4.

TABLE 4 MEANS, SD (IN PARENTHESIS) AND RESULTS OF ANALYSIS OF VARIANCE FOR THE 5 GROUPS ON TESTS IN THE PHASE 2 EXPERIMENT

Group	*Digit Span*	*Verbal IQ*	*LP (immed.)*	*LP (delay)*
	*	F = 1.06, n.s.	F = 1.12, n.s.	F = 1.22, n.s.
NT	15.1 (3.3)	105.7 (8.9)	18.1 (7.1)	13.7 (5.2)
GR	15.3 (3.2)	114.7 (14.7)	18.2 (4.9)	14.7 (3.6)
FA	17.1 (3.4)	114.7 (8.6)	17.5 (3.1)	14.1 (3.6)
PR	15.3 (3.7)	107.5 (12.2)	15.7 (4.5)	10.2 (5.9)
NC	16.4 (4.3)	111.8 (12.4)	21.2 (7.2)	15.2 (7.2)

	VR (immed.)	*VR (delay)*	
	F = 2.0, n.s.	F = 2.13, n.s.	
NT	7.8 (5.2)	7.2 (5.0)	RAVLT Recognition $\chi^2 = 7.32$, n.s.**
GR	9.0 (3.1)	7.8 (3.0)	DRT Word List: $\chi^2 = 7.08$, n.s.**
FA	8.2 (2.3)	7.6 (3.2)	Block Test: $\chi^2 = 4.52$, n.s.**
PR	5.1 (2.3)	4.2 (2.6)	Item 99 $\chi^2 = 6.28$, n.s.**
NC	9.4 (3.5)	8.6 (3.3)	Map Test. $\chi^2 = 4.30$, n.s.**

* Not analysed statistically; ** Analysed nonparametrically. LP = Logical Passages (WMS); VR = Visual Reproduction (WMS); RAVLT = Rey Auditory Verbal Learning Test (recognition). For Group abbreviations, *see* Table 1.

No significant differences on any test administered in Phase 2 were observed in any of the groups. Despite the constant tendency of Group PR to obtain the lowest scores on the majority of tasks, all PD group results were comparable statistically with the normal group. Group PR clearly did not reveal selective impairment for attentional processes (Digit Span) which might have contributed to lower scores on the tests in Phase 1, nor did any group exhibit evidence of cognitive dysfunction in language processes (WAIS-R), memory (WMS tests, RAVLT recognition, DRT word list), or visuospatial functions (Block test, Item 99, Map test).

DISCUSSION

In well-matched, representative, and statistically adequate PD patient groups identified by treatment response, impairment in a selective cluster of executive tasks sensitive to frontal lobe dysfunction (WCST, RAVLT and BTap) emerged in the early untreated group of patients, and in the two groups which continued to respond to medication. These results were expected on the basis of an earlier study (Taylor *et al.*, 1986*a*). Good responders were also impaired on the DRT spatial list, while the performance of the group with fluctuations and dyskinesias (AIMs) almost reached significance. Deficits on all these tests were observed in the Poor Response group with secondary treatment failure where impairment was more profound, distinguishing performance from other PD groups on all but the WCST. This group-specific profile was augmented by deficits on VF and TMT, a finding unique to the Poor Response group. No additional deficits were observed in any group despite extensive testing of attention, sustained concentration, immediate and delayed recall of verbal and visual material, recognition memory for lists of words, and complex visuospatial processes involving reasoning, mental rotation, and egocentric orientation. Moreover, current intellectual status, measured by the verbal section of WAIS-R was statistically equivalent in all groups.

Tests 1–4 place maximal demands on mental or motor planning when a unique set of task-specific contingencies must be acquired in order to problem solve. A deficit in strategic planning under novel conditions appeared to characterize all four PD groups. However, the deficit was somewhat more profound and extensive in poor responders, as even tasks which depend upon familiar information to facilitate obvious cognitive strategies (5, 6) were disrupted. In this case it seems reasonable to assume that patients who no longer maintain an obvious response at any time during the course of treatment are at greater cognitive risk.

It is interesting to note that, despite considerably longer disease duration, and maximum severity during 'off' periods, the group of patients with fluctuations and abnormal involuntary movements maintained a cognitive profile equal to the No Treatment and Good Response groups on all the cognitive measures. For this reason no simple relationship between disease duration, disease severity and the observed deficits was found. Indeed, had the patients with positive complications not been assessed exclusively during periods of maximal treatment benefit, scores on the Purdue test, representing severity, would have been considerably more impaired than in any other group. Nevertheless, these individuals retain intact cognitive function on all but a select cluster of tasks despite frequent marked swings in physical status. Testing during both 'on' and 'off' states in 5 additional patients, using alternate test forms, revealed no significant alteration in cognitive status consequent upon physical state, consistent with the findings of Delis *et al.* (1982) and Brown *et al.* (1984).

The tight coupling of disease duration/treatment duration in the Poor Response group suggested the possibility of distinct features in the early history prompting relatively rapid institution of treatment. However, retrospective consideration of the reported symptoms at onset in these 9 patients failed to detect any consistent or unique themes. In 4 cases, PD was heralded by tremor; the remaining 5 patients presented with akinesia and rigidity. In this respect they were typical of the PD group as a whole. Three suffered a rapid progression; the remaining 6 progressed at a moderate rate. Four displayed a good initial treatment response while 5 responded in a moderately favourable manner. In this group, later treatment failure was not associated with any clear predictive signs.

While the mechanisms responsible for secondary treatment failure remain poorly understood (Yahr, 1984), it is quite possible that individuals vary considerably in their ability to tolerate antiparkinsonian agents which, themselves, disrupt the natural physiological compensatory mechanisms such as increased presynaptic dopamine turnover and denervation supersensitivity of postsynaptic receptors (Hornykiewicz, 1979). Intrinsic factors may dictate the rate at which disease evolves making some patients more vulnerable to the interactive effects of drugs and the underlying pathophysiology. In this respect the shorter duration of disease in the Poor Response group compared with the other two treated groups may reflect lesser underlying physiological plasticity. Alternatively, despite remaining typical with respect to symptomatology at this time, it is possible that additional, and/or differentiable pathology will emerge later, then reflected, in part, by more extensive disruption of processes sensitive to the integrity of the frontal lobes.

At the time of neuropsychological testing there was no evidence of generalized cognitive decline in the Poor Response group to suggest an early dementia. However, despite comparable levels of performance on the WAIS-R verbal tests, and Digit Span, results of all other tests in Phase 2 reflected a consistent though nonsignificant trend toward lowered performance in this group. With regard to spared abilities, it is well known that many functions sampled by the Wechsler Intelligence Test are relatively 'stable', and that, of all the cognitive measures employed, the verbal IQ is probably the least sensitive to cerebral dysfunction due to the highly structured and familiar nature of the material involved (Milner, 1982). Moreover, although visuospatial testing revealed no selective deficit in the Poor Response group, the rate of processing was observed to be selectively slower, suggesting that efficiency in this domain was compromised. Sex differences in the five groups (noted to be a strongly contaminating factor in visuospatial processing rate in a previous study (Taylor *et al.*, 1986*a*)), prevented adequate analysis of this issue. However, on the Trail-Making Test, where the influence of motor speed was eliminated and sex differences are not contributory, a massive prolongation in mental processing time was evident in the Poor Response group. The effect was sufficiently marked to suggest that, with respect to rate of information processing on tasks sensitive to frontal lobe function, poor responders may belong to a distinct subgroup. This is supported by the extent of their deficits on frontal lobe-based tests and by their consistent tendency to perform at levels below all other groups, despite adequate attention to tasks.

Careful monitoring of this group in life and post-mortem neuropathological study should help clarify the ultimate significance of secondary treatment failure and the related cognitive deficits. It is possible that the combination of declining response and extensive loss of executive functions heralds the development of a later dementia of the Alzheimer type as described by Lieberman *et al.* (1979). However, the absence of significant memory disorders in the Poor Response group, such as characterize the early stage of Alzheimer's disease (Rosen and Mohs, 1982), makes this doubtful. Alternatively, over time, the classical picture of PD now observed in secondary treatment failure may evolve into a more complex syndrome as additional symptoms emerge to suggest an alternate diagnosis. Failing this, it is possible that poor responders, without evidence of concurrent dementia, and who remain typical with respect to symptom presentation, may suffer a greater loss of plasticity in terms of 'turnover rate' and/or number and sensitivity of receptor sites within the dopaminergic system. Dopamine thresholds or compensatory resilience may affect other putative transmitters, which conceivably participate in the complex processes of basal ganglia activity (Hornykiewicz and Kish, 1984). In this case, lost response to treatment and extensive involvement of frontal lobe-based cognitive functions may reflect differentiable pathophysiological correlates compared with individuals who continue to respond to pharmacotherapy and maintain a higher level of cognitive integrity. Maintained plasticity, even if complicated by positive motor symptoms, may explain the ability of group FA to confine cognitive deficits within the same cluster as the less disabled patients.

In this regard, Rinne (1982) has observed important relationships between clinical variables and changes in striatal dopamine receptors. Fluctuations and AIMs were associated with an increase in receptor number, revealed through ^{3}H-spiperone binding studies in PD brains, while a deteriorating response to treatment was associated with a decrease in the number of these receptors. Moreover, cholinergic activity in striatal and cortical areas was related to the quantity of dopamine receptors. In PD patients with a low number of dopamine receptors, labelling of cholinergic muscarinic receptors revealed decreased numbers in both the caudate nucleus and cortex. Individuals with increased dopamine receptors displayed evidence of a corresponding increase in cholinergic receptors. The association between receptor counts in the two neurotransmitter systems was similar in treated and untreated patients. As cortical cholinergic status has been implicated in the cognitive function of PD patients (Javoy-Agid *et al.*, 1984), poor responders may be at additional risk through a linked loss of receptors for dopamine and acetylcholine.

Alternatively, additional mechanisms may be implicated in the failure to respond to treatment. According to Marsden and Parkes (1977), it is possible that the natural progression of the disease itself includes pathological changes within the striatum, globus pallidus and possibly the cortex.

The distribution of residual dopamine within the striatum of PD patients becomes critical to cognitive function in terms of the ability to affect frontocaudate circuits within the complex loop which ultimately returns information processed in the caudate nucleus to the prefrontal cortex (DeLong *et al.*, 1983). In a recent PET scan study, imaging of dopaminergic activity in 11 early nondemented PD patients, revealed that dopamine depletion was significantly more marked in the putamen than in the caudate nucleus where concentrations remained within normal limits (Nahmias *et al.*, 1985). It appeared that, in the early stages, tremor, rigidity and bradykinesia could be accounted for by diminished dopaminergic activity in the putamen alone. Presumably, the normal concentration of dopamine in the caudate nucleus supported intact mentation. This physiological independence of the two striatal nuclei is consistent with the concept of segregated and parallel cortico-striato-thalamo-cortical motor and complex loops (DeLong *et al.*, 1983), which now can be seen to undergo differential rates of dopaminergic dysfunction in living patients in the early stage of disease.

A word of caution must be inserted concerning the normality of mentation in those patients, all of whom were tested neuropsychologically by the present authors. They were not demented. However, like the four PD groups in the present study, a subtle deficit involving strategic planning was present (WCST), although not apparent unless specifically explored by formal testing. As the deficit was present despite 'normal levels of dopamine' within the caudate on PET scanning, this implies that the present resolution of this technique is insufficient to detect subtle physiological changes.

In more advanced patients, regional differences in the striatal distribution of dopamine have also been observed. In a recent pathological study Kish *et al.* (1986) have described important dissociations between the areas of the caudate nucleus and putamen depleted in PD. Interestingly, in the caudate, maximal dopamine reduction occurred in the anterodorsal head of this structure, the area which receives a massive projection from the prefrontal cortex and, in particular, the lateral convexity (Rosvold, 1972). In animal experiments, damage to the anterodorsal head of the caudate has been associated with deficits in the performance of cognitive tasks which demand the formation and retention of subjectively organized plans (Johnson *et al.*, 1968), demands similar to task-specific conditions under which patients with PD demonstrate selective impairment.

Changes in the mesocortical dopaminergic system must also be considered in the cognitive profile in relation to treatment response. Scatton *et al.* (1982) have demonstrated that, in PD, Brodmann's area 9 suffers a reduction in dopamine content. The magnitude of this depletion in the analysed brains was minor (19%) compared with reported losses in the putamen (80%+) and caudate (60%+) (Hornykiewicz, 1980). Moreover, almost total destruction (89%) of the dopamine terminations in the sulcus principalis was required to produce a significant cognitive deficit in monkeys (Brozoski *et al.*, 1979). Despite the foregoing, it is possible that secondary treatment failure is partly dependent on deterioration of the mesocortical dopaminergic system as well, further undermining the integrity of frontal lobe-based behaviours.

Indeed, in a recent post-mortem study of 4 patients, cell counts within the ventral tegmental area revealed that between 36–55% of the dopaminergic cells which project to the prefrontal cortex were destroyed (Uhl *et al.*, 1985). However, as those patients were not rated for response to treatment, or formally evaluated neuropsychologically, it is unclear what role treatment variables played in the implied association between cell loss in the ventral tegmentum and mental changes.

In conclusion, the relationship between mental and motor alterations in PD remains far from simple. Patients with severe fluctuations in motor status can retain a level of cognitive function equivalent to their untreated or well-controlled age and IQ-matched peers. Those who develop secondary treatment failure do not differ significantly from all other groups or from normal control subjects on intellectual, visuospatial and mnestic functions not primarily dependent upon frontal lobe functional integrity. Thus the ability to respond to dopamine replacement or agonist therapy, even if intermittently, appears more important than duration of disease, length of treatment, or severity of motor impairment, in predicting the probability and severity of cognitive impairment.

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CHRONIC DEMYELINATING PERIPHERAL NEUROPATHY ASSOCIATED WITH MULTIFOCAL CENTRAL NERVOUS SYSTEM DEMYELINATION

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SUMMARY

A series of 6 cases is described in which a chronic demyelinating neuropathy was associated with a relapsing multifocal CNS disorder, the clinical features of which resembled multiple sclerosis. Multifocal CNS lesions were demonstrated by CT and MR imaging and the presence of CNS demyelination was indicated by prolonged central conduction times. These cases are discussed in relation to the occurrence of combined peripheral and central demyelination in chronic relapsing experimental allergic encephalomyelitis and neuritis.

INTRODUCTION

Acute idiopathic demyelinating polyneuropathy (AIDP) or the Guillain-Barré syndrome consists of an acute or subacute demyelinating disorder characterized by the presence of multifocal areas of demyelination in the peripheral nervous system (PNS), associated with inflammatory infiltrates. These are predominantly located in the spinal roots but are present throughout the PNS (Asbury *et al.*, 1969). The earlier literature contains references to examples of chronic progressive or chronic relapsing polyneuropathy, some of which showed evidence of hypertrophic (onion bulb) changes, betraying their chronic demyelinating nature (Roussy and Cornil, 1919; Nattrass, 1921), or which were corticosteroid-responsive (Austin, 1958; Hinman and Magee, 1967; Dyck *et al.*, 1968). Thomas *et al.* (1969) and Dyck *et al.* (1975) demonstrated that such cases showed extensive demyelination in teased fibre preparations, sometimes with associated hypertrophic changes, and that inflammatory infiltrates could be demonstrated both in peripheral nerve trunks and in spinal

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roots. These cases are now designated as chronic idiopathic (or inflammatory) demyelinating polyneuropathy (CIDP). The underlying disease mechanisms are not yet understood, either in AIDP or CIDP, but the justification for linking them depends upon their clinical and pathological similarities. Both the acute and chronic forms tend to involve motor function to a greater extent than sensation and, in both, the CSF protein content is usually elevated, often substantially. Observations on nerve conduction demonstrate not only reduced conduction velocity related to demyelination and remyelination, but sometimes focal conduction block consistent with the multifocal nature of the pathological changes. The clinical overlap extends to instances where patients with an initial acute monophasic illness consistent with AIDP subsequently progress to a chronic relapsing course (Thomas *et al.*, 1969). Until the nature of the causal mechanisms is understood more precisely, the significance of these overlapping clinical and pathological features will remain uncertain. There may be genetic differences between patients with the two types of disease. No consistent differences in the distribution of HLA antigens have been found between AIDP and normal populations (Adams *et al.*, 1977), whereas a tendency for patients with chronic relapsing demyelinating polyneuropathy to show an HLA-A1, -B8, -DW3, -DR3 haplotype was reported (Stewart *et al.*, 1978; Adams *et al.*, 1979). More recent observations have suggested an association between CIDP and the HLA-A3 and -DR2 antigens (McLeod, 1986), which are also associated with multiple sclerosis (MS) (McDonald, 1984).

The present series of 6 cases all had a chronic demyelinating neuropathy with features consistent with CIDP but, in addition, showed evidence of CNS involvement often with a relapsing multifocal course resembling MS. There have been occasional reports in the past of hypertrophic changes in the spinal roots of patients with MS, sometimes associated with infiltrates of inflammatory cells (Dinkler, 1904; Schob, 1923; Ketelaer *et al.*, 1966; van Gehuchten, 1966; Ninfo *et al.*, 1967; Jellinger, 1969; Schoene *et al.*, 1977; Rosenberg and Bourdette, 1983). There is also a single report of pathologically established acute MS in combination with an inflammatory demyelinating neuropathy (Lassmann *et al.*, 1981*a*). In another report, a patient with clinical features suggestive of MS developed a demyelinating neuropathy confirmed by the finding of hypertrophic changes in a sural nerve biopsy (Ro *et al.*, 1983). The concurrence of CNS and PNS demyelination in such cases clearly raises questions related to underlying disease mechanisms.

CASE REPORTS

The 6 cases consisted of 2 women and 4 men with ages of onset of first symptoms ranging from 19 to 44 years. All were Caucasian and none except Case 3 had a relevant family history.

Case 1 (NH no. A51890)

S.H., a man aged 28 years, experienced blurred vision for one month in 1962 and a recurrence for two months in 1964. In May 1968, when aged 34, he developed excessive fatigue after vigorous exercise, and subsequently a fluctuating cold sensation over both knees. In July 1968, loss of sensation in his left leg developed when running, with resolution when he walked. Over the ensuing months tingling and burning paraesthesiae spread progressively from his toes up his legs, and affected his fingers. He was admitted to hospital in November 1968. Distal weakness, tendon areflexia and distal sensory loss were recorded. He received no treatment, recovered spontaneously, and was able to return to work in February 1969, having no symptoms other than numbness in his right hallux by August 1969. In December 1969, he suffered nausea and vomiting for six days. He became constipated. Three weeks later, he developed pain and numbness in the lower abdomen, weakness and numbness in both legs, back pain, loss of sensation of bladder fullness, difficulty initiating micturition, and failure of orgasm and ejaculation. All these symptoms came on over a period of a few weeks. He was admitted to the National Hospital in January 1970.

He was unable to walk, with a paraparesis and bilaterally extensor plantar responses. All his tendon reflexes were present. He had sensory loss in both legs with a level on his trunk at T10 dermatome. Recovery started before ACTH injections were given but accelerated shortly after the injections started. At follow-up in June 1970 he had only sensory symptoms in his legs. He was walking. The plantar responses were flexor.

Between 1970 and 1975 he had approximately eight relapses and received six courses of ACTH. In December 1975 a relapse rendered him so weak that he required hospital admission. Alternate-day prednisolone was started and he continued this in small doses over the next nine years. During 1982, he took azathioprine (100 mg daily). His symptoms fluctuated in severity, consisting of impotence, bladder and bowel disturbance, weakness and sensory loss. He had occasional visual blurring, and an episode of double vision. He was reassessed at the National Hospital in November 1984, at which time he was able to walk 100 m.

Visual acuity and colour vision were normal. The right optic disc was pale. He had bilateral ptosis. There was wasting of the small hand muscles, and the forearm flexors and extensors and small hand muscles were weak. Wasting affected anterior tibial compartment muscles and extensor digitorum brevis bilaterally. In the legs there was proximal as well as distal weakness. Ataxia was more marked in left-sided limbs than on the right. Upper limb tendon reflexes could be obtained with reinforcement. Lower limb reflexes were absent. The plantar responses were both extensor. There was distal cutaneous sensory loss and impaired joint position and vibration sense in his toes. The peripheral nerves were thickened asymmetrically (fig. 1). Following a course of ACTH injections, proximal leg power improved.

Case 2

C.P., a woman, had noted intermittent tingling and alteration of sensation in her legs from the age of 21 years. In 1973, when aged 33, there was an episode of sensory disturbance affecting both hands with a recurrence in 1978, and a further relapse later the same year which was followed by weakness of her hands and legs and impaired bladder and bowel function. On admission to hospital, examination revealed generalized weakness. The biceps and brachioradialis tendon reflexes were depressed or absent, the triceps and knee jerks being brisk and the ankle jerks absent. Plantar responses were equivocal. Sensory loss affected all four limbs with asymmetry in the legs suggesting a left-sided spinal cord lesion. Myelography and CSF were normal. Substantial improvement followed a 10-day course of tetracosactrin. In February 1979 she relapsed, developing marked incoordination and loss of balance over a few days, with pain in her throat and ears. There was only mild limb weakness. The tendon reflexes were all brisk except for the right ankle jerk which required reinforcement. Severe sensory loss, particularly proprioceptive, affected all limbs. She was again treated with tetracosactrin, with improvement. When first seen at the National Hospital, in March 1979, she had sensory symptoms only. There was a mild spastic paraparesis. All tendon reflexes were present. There was distal loss of joint position sense and vibration sense. Over the next three years she deteriorated, including at least two relapses with incomplete recovery. In June 1979, a relapse comprised deterioration of gait, increasing

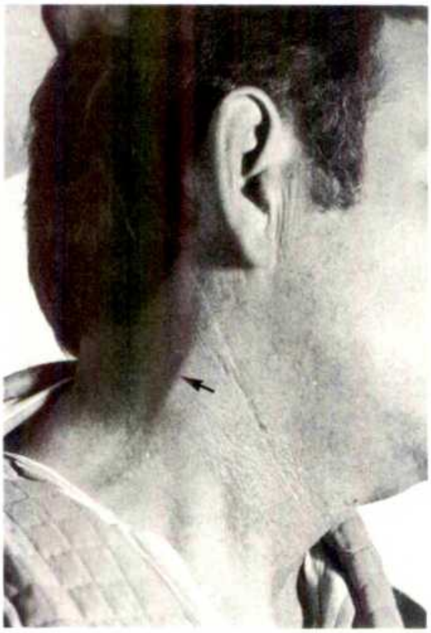

FIG. 1. *Case 1*. Enlargement of greater auricular nerve (arrow).

clumsiness of her hands with inability to write, urgency of micturition and blurring of vision. By April 1980, she required a wheelchair. During 1980 she complained of pain in her arms and legs. On admission to the National Hospital in August 1982, she could walk only 20 m. There was generalized muscle wasting and weakness. The tendon reflexes could all be obtained, some only with reinforcement. Both plantar responses were extensor and there was distal sensory loss in the limbs. The peripheral nerves were markedly thickened. She received a course of ACTH injections.

By January 1983 her strength had improved. She started alternate day prednisolone and azathioprine (100 mg daily). During 1983 overall slow improvement in her gait was recorded. In July 1983 she was able to walk without a stick. Over the next two years her neurological condition was fairly stable.

Case 3

E.E., a man aged 33 years, developed headache, blurred vision and diplopia. His symptoms resolved within five weeks. A year later, in September 1979, he had a second attack of double vision, followed some weeks later by impairment of his sense of taste. When examined in November 1979, he had a right internuclear ophthalmoplegia. Two weeks later, he developed weakness of his legs and unsteadiness, although his double vision cleared. Gait ataxia and spasticity, and weakness of the left leg were noted. His symptoms resolved without treatment. In 1981 he complained of urgency of micturition with incontinence and impotence. Over the three months before his first admission to the National Hospital in October 1981 there was progressive weakness of his legs. There had been no response to a 25-day course of ACTH injections. On admission he was unable to stand. There was generalized muscle wasting, reduced muscle tone and generalized weakness, distal more than proximal. The upper limb tendon reflexes were present, but the abdominal reflexes, lower limb reflexes and plantar responses were all absent. There was distal impairment of cutaneous sensation in the limbs and absence of vibration sense in the legs.

He was given prednisolone (60 mg on alternate days) and azathioprine (3 mg/kg daily). By December 1981 he was standing with difficulty. During 1982 his strength improved and his lower limb tendon reflexes returned. The dosage of prednisolone was reduced. In November 1982 he suffered a relapse with diplopia, unsteadiness of gait and tingling paraesthesiae in the lower limbs. He was dysarthric and had bilateral lateral rectus palsies. There was muscle wasting and distal weakness, but the tendon reflexes were brisk. The plantar responses were both extensor. Sensory loss was more extensive than previously.

Following an increase in the dosage of prednisolone, he again improved. During 1983 and 1984 he remained well despite reducing doses of prednisolone, but in November 1984 he developed a relapse of the central component of his illness with a worsening spastic paraparesis without apparent response to augmented prednisolone dosage.

His maternal half-sister and maternal uncle both had multiple sclerosis. Nerve conduction studies in the former showed no evidence of peripheral neuropathy.

Case 4

J.G., a man aged 38 years, developed tingling paraesthesiae in both hands in April 1980, which resolved after three months. In November 1980 he experienced discomfort in the sole of the left foot. In January 1981 he developed gait disturbance, sensory loss in his limbs and exertional pain in his legs. He became unsteady and weak, and described oscillopsia. Painful feet became his predominant symptom. When examined at the National Hospital in November 1981 he was disinhibited, dysarthric and ataxic, with bilateral foot drop. The right optic disc was pale. Ocular flutter was noted. Pursuit eye movements were broken up. He had a right internuclear ophthalmoplegia. There was failure of suppression of the vestibulo-ocular reflex. The small hand muscles and both quadriceps muscles were wasted. Fasciculations were seen in quadriceps. There was mild/moderate generalized weakness. All limbs were ataxic, with postural as well as action tremor. The tendon reflexes were depressed or absent. The plantar responses could not be elicited because of the hypersensitivity of the soles of his feet. Sensation in the upper limbs was normal. There was distal cutaneous sensory loss in both legs with impaired joint position sense in the toes. The peripheral nerves were thickened. After investigation, azathioprine (100 mg daily) was started. He reported improvement in the pain in his feet four days after starting treatment. However, by December 1982 he complained of increasing tremor, and pain in his feet prevented him from walking more than a few yards. Examination revealed the same signs as previously, except that his internuclear ophthalmoplegia had resolved, but his intention tremor had become worse. When admitted for review in February 1984, his feet were less hypersensitive than they had been. He remained ataxic, but there was only minimal distal weakness in his arms and legs. The peripheral nerves were markedly thickened. In February 1984 his condition was largely unchanged. Disinhibition was again noted.

Case 5

In 1980, P.G., a 41-year-old man, developed intermittent double vision. In 1982 he began to notice impaired concentration and difficulty in reading. Over the next year his balance deteriorated and he started to have falls. He had difficulty judging distances, twice crashing a vehicle while reversing. On admission to hospital in June 1983 he felt depressed and exhausted. He complained of poor memory. He was mentally slow. There was evidence of mild global intellectual deterioration. His gait was ataxic. He had bilateral internuclear ophthalmoplegia. There was mild left facial weakness and tongue movements were slow. Mild pyramidal weakness and ataxia affected the right arm and leg. Upper limb tendon reflexes were normal, but the knee jerks were pathologically brisk; the ankle jerks required reinforcement and the plantar responses were absent. Joint position sense was impaired in the toes and the fingers of the right hand. Vibration sense was absent in the right upper limb and impaired distally in both feet. The two-point discrimination threshold was raised in the fingers of the right hand. Otherwise sensation was normal.

He was readmitted in November 1983, by which time pain affecting both feet and both hands had become a significant symptom. He complained of weakness of the left hand. His balance was worse. He used a stick and could walk only half a mile. Fatigue remained a prominent feature. On examination, he was now dysarthric, and left-sided facial weakness was more obvious. Weakness affected all four limbs. The ankle jerks were depressed but other tendon reflexes remained brisk; the right plantar response was extensor. Joint position sense was more severely impaired in the right hand than previously, and there was patchy loss for pin prick in the right arm.

Case 6

In 1973 S.M., a 29-year-old woman, had a two-week episode of 'dizziness'. Two years later she experienced numbness of the right leg for one month. In the following year, she totally lost vision of the right eye over a few days. A diagnosis of retrobulbar neuritis was made, but in addition a mild paraparesis was noted. The CSF was normal. She was treated with a course of ACTH. After initial deterioration, including retention of urine and increasing weakness and numbness of the left leg, she improved. Her vision recovered within two weeks and was completely normal within three months. Over the next two years she had a number of episodes of dizziness, double vision, weakness of her limbs and unsteadiness, with partial or complete recovery between attacks, but her spastic paraparesis was observed to become progressively more severe. When first admitted to the National Hospital in July 1978, she had just suffered an episode of numbness of the left cheek and jaw and left side of her tongue. She used a stick and could walk only 15 m. She was dysarthric and ataxic. The right optic disc was pale. Pursuit eye movements were jerky. There was first degree nystagmus to the right, left facial sensory loss, mild weakness of the left arm and hand, and a moderate asymmetric paraparesis, left worse than right. The tendon reflexes were all obtained, but the knee reflexes required reinforcement. The plantar responses were both extensor. Vibration sense was absent in the legs. There was distal sensory loss for light touch and pin prick in the limbs. From July 1978, for two years, she received 2.5 mg/kg azathioprine daily.

Between 1978 and 1981 she progressively lost her tendon reflexes, and developed increasing weakness, ataxia, titubation and sensory loss. In October 1981 she had a generalized convulsion, with four further seizures over the next year. Seizures continued at a rate of one every two months approximately, in spite of anticonvulsant medication. In July 1983, fever and dehydration necessitated acute hospital admission, where hyperglycaemia was found. She required intravenous insulin. Having recovered, oral glibenclamide caused a hypoglycaemic attack and her diabetes was treated by diet alone.

In September 1983 she was reassessed at the National Hospital. She was unable to walk, or feed or wash herself because of weakness and action tremor. She was euphoric, but memory and mental arithmetic were good. She was dysarthric. There was impaired colour vision and optic disc pallor bilaterally. She had bilateral internuclear ophthalmoplegia and impaired upgaze. Proximal and distal limb muscles were markedly wasted. The limbs were flaccid, apart from clonus at both ankles. Weakness of all muscle groups was severe. Gross postural and action tremor affected both upper limbs. She was totally areflexic. The plantar responses were extensor. Joint position sense and vibration sense loss affected all four limbs, but cutaneous sensation was preserved. The peripheral nerves were thickened.

Over the next six months, she received prednisolone (60 mg on alternate days) with no improvement. There was no hyperglycaemia in spite of the corticosteroid administration and her previous acute episode of hyperglycaemia. She remained stable until April 1985 when she suffered another relapse with double vision, worsening articulation and increased weakness.

INVESTIGATIONS

Haematological and biochemical findings in all 6 cases, except for the development of transient diabetes mellitus in Case 6, were unremarkable. In Case 5 leucocyte aryl sulphatase A activity was 25 nmol/mg protein/h, which is reduced, but not within the range for homozygotes with metachromatic leucodystrophy (0–12 nmol/mg protein/h).

TABLE 1. MOTOR NERVE CONDUCTION

Case	Date of examination	*Median nerve*		*Ulnar nerve*		*Peroneal nerve*	
		DML *(ms)*	*MCV* $(m\cdot s^{-1})$	*DML* *(ms)*	*MCV* $(m\cdot s^{-1})$	*DML* *(ms)*	*MCV* $(m\cdot s^{-1})$
1	Nov. 1968	4	16	ND	ND	4	26
	Jan. 1970	4	25	ND	ND	6	27
	May 1973	5	27	ND	ND	4	29
	Dec. 1975	5	37	ND	ND	6	39
	Feb. 1982	5	32	ND	ND	5	27
	Nov. 1984	4	30	4	30	8	24
2	Dec. 1978	NA	39	NA	52	NA	31
	Feb. 1979	4	40	3	45	5	45
	Aug. 1982	5	35	5	15	7	18
	Mar. 1985	ND	ND	3	32	8	23
3	Oct. 1981	17	28	10	27	NR	NR
	Nov. 1982	10	28	ND	ND	NR	NR
4	Nov. 1981	ND	ND	9	19	22	ND
	Dec. 1982	16	19	10	15	ND	ND
	Feb. 1984	14	11	11	17	ND	ND
5	June 1983	6	31	4	34	10	24
	Oct. 1983	ND	ND	5	25	15	23
6	Sep. 1983	24	20	ND	ND	NR	NR
	Jan. 1984	17	17	19	26	ND	ND
	Mar. 1984	ND	ND	11	14	ND	ND

DML = distal motor latency; MCV = motor conduction velocity;
NR = no response; ND = not done; NA = not available.

TABLE 2. SENSORY NERVE ACTION POTENTIAL AMPLITUDE (μV)

Case	*Date of examination*	*Median nerve*	*Ulnar nerve*	*Sural nerve*
1	Dec. 1968	—	ND	ND
	Jan. 1970	1	ND	ND
	May 1973	6	ND	ND
	Dec. 1975	—	—	ND
	Feb. 1982	—	—	—
	Nov. 1984	—	—	—
2	Aug. 1978	14	5	ND
	Dec. 1978	7	6	ND
	Feb. 1979	10	6	ND
	Aug. 1982	2	6	—
	Mar. 1985	13	2	2
3	Oct. 1981	—	—	—
	Nov. 1982	—	2	—
4	Nov. 1981	—	—	—
	Dec. 1982	—	—	ND
	Feb. 1984	—	—	ND
5	June 1983	4	2	7
	Oct. 1983	2	ND	ND
6	Sep. 1983	—	—	—
	Jan. 1984	—	ND	—
	Mar. 1984	—	—	ND

— = absent; ND = not done.

Electrophysiology

Muscle sampling revealed electromyographic evidence of denervation in affected muscles in all patients except for Case 5. The results of motor and sensory nerve conduction studies are given in Tables 1 and 2. All cases showed substantially reduced motor nerve conduction velocity and increased distal motor latencies, consistent with demyelination, in one or more nerves. Sensory nerve action potentials were consistently absent or of reduced amplitude except in the median nerve on some occasions in Case 2.

The results for visual (VEP) and somatosensory (SEP) evoked potentials are summarized in Tables 3 and 4. Prolonged VEP latencies on one or both sides were obtained in all patients except Case 3, in which, however, the latency of the second set of responses had increased by 9 ms, which is abnormal. Borderline values were recorded in Case 2. The N9 component of the SEP was absent or delayed at some stage in all cases, confirming a peripheral abnormality. Where recordings could be

TABLE 3. VISUAL EVOKED POTENTIALS (FULL-FIELD PATTERN REVERSAL)

Case	*Date of examination*	*Eye*	*Latency* (ms)*	*Amplitude (μV)*
1	Dec. 1975	L	94	10.8
		R	120	10.4
	Feb. 1982	L	97	10.9
		R	126	7.2
	Nov. 1984	L	116	9
		R	134	7
2	Aug. 1982	L	114	10
		R	112	11
	Mar. 1985	L	115	11
		R	114	11
3	Aug. 1981	L	96	13
		R	96	12
	Nov. 1982	L	105	9
		R	105	10
4	Nov. 1981	L	106	11.4
		R	163	9.4
	Dec. 1982	L	109	12.5
		R	170	8.8
	Feb. 1984	L	106	9.5
		R	167	8.4
5	June 1983	L	uncertain†	uncertain†
		R	uncertain†	uncertain†
6	July 1978	L	115 (155)**	3 (2.1)
		R	115 (148)**	3.1 (5.5)
	Nov. 1979	L	115 (162)**	3.1 (6.3)
		R	163	11

* P100 component (normal range < 114 ms); ** positive-negative-positive wave forms; † ill-formed waves.

obtained, the N20 component was delayed, sometimes considerably, in all patients except Case 5. Brainstem auditory evoked potentials showed abnormalities indicative of brainstem lesions in Cases 4 and 5. In Case 4, wave I had a normal latency on the right (2.1 ms), but waves II, III and V were absent, suggesting a right brainstem lesion; normal values were obtained on the left. In Case 5, latencies for wave V and the I–V intervals were normal on both sides, but the middle waves (II–IV) were not detected on the right, again suggesting a brainstem lesion on that side. In Case 3 there was a delay for wave I, indicating a peripheral lesion.

TABLE 4. SOMATOSENSORY EVOKED POTENTIAL LATENCIES TO MEDIAN NERVE STIMULATION (MS)

Case	*Date of examination*	*Eye*	*N9*	*N13*	*N20*
1	Nov. 1984	L	—	—	31.0
		R	—	—	35.1
2	Aug. 1982	L	19.8	—	49.7
		R	—	—	46.4
	Mar. 1985	L	13.4	—	34.0
		R	14.0	—	39.6
3	Oct. 1981	L	—	—	26.8
		R	—	—	26.8
	Nov. 1982	L	13.1	17.6	24.8
		R	13.1	17.4	24.2
4	Nov. 1981	L	—	—	40
		R	10.8	—	28.3
	Dec. 1982	L	—	—	38
		R	—	—	30.1
5	May 1983	L	9.4	—	20
		R	—	—	—
6	July 1978	L	8.6, 9.6	15.7	27.6
		R	8.8, 10.0	12.5	24
	Nov. 1979	L	10	13.2	26.6
		R	9.5	13.2	24.7
	Sep. 1983	L	—	—	—
		R	—	—	—
	Dec. 1984	L	—	—	—
		R	—	—	—

L = left; R = right; — = absent.

Conduction in central and proximal peripheral motor pathways was assessed in 3 patients (Cases 1, 2, 4, 6) using the technique of percutaneous stimulation over the scalp and vertebral column (Merton and Morton, 1980; Cowan *et al.*, 1984; Mills and Murray, 1985*a*, *b*, 1986). The results are presented in Table 5 and fig. 2. Considerably prolonged or absent responses were obtained in all 4 patients. The findings in Case 1 have been reported in greater detail by Mills and Murray (1986).

TABLE 5. PERIPHERAL AND CENTRAL MOTOR CONDUCTION (UPPER LIMB)*

Case	*Ulnar conduction velocity* (m·s^{-1}) Elbow-wrist	Axilla-elbow	C7-axilla	*Central conduction time* (*ms*) Cortex-C7
1	30.3	21.7	21.9	10.2
2	34.1	25.7	36.2	15.0
4	20.4	27.4	30.0	10.0
6	19.6	26.9	42.8	NR
Mean normal	61.1	64.3	78.5	4.4
SD	4.2	8.5	9.6	0.75

* Recording electrodes on abductor digiti minimi with stimuli to ulnar nerve at wrist, elbow and axilla, over cervical spine and to contralateral motor cortex. NR = no consistent response obtained.

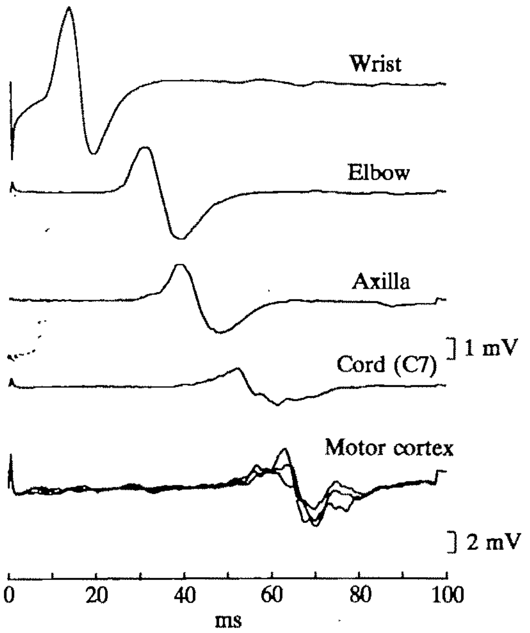

FIG. 2. *Case 4*. Measurement of central conduction time and peripheral conduction velocity. Muscle action potentials were recorded from abductor digiti minimi on supramaximal stimulation of the ulnar nerve at the wrist, elbow, axilla and over the spinal cord at C7. Stimulation over the hand area of the contralateral motor cortex resulted in small muscle responses. The latency difference between cortex and cord responses of 10.0 ms is more than twice the upper limit of normal. Peripheral motor velocity is also reduced at between 20 and 30 m·s^{-1}.

TABLE 6. DISTRIBUTION OF LESIONS ON NUCLEAR MAGNETIC RESONANCE IMAGING

Case	*Brainstem*	*Cerebellar*	*Periventricular*	*Cerebral*
1	—	—	+	+
2	—	—	+	—
3	+	+	+	+
4	+	+	+	+
6	+	+	+	+

Neuroimaging

Computed tomographic (CT) x-ray cranial scans were performed in all 6 patients. No abnormalities were detected in Cases 3 and 4. Cerebral atrophy was evident in Cases 1, 2 and 6 and cerebellar atrophy in Cases 5 and 6. In addition, focal low density lesions were observed in Cases 1, 2, 5 and 6 which were periventricular in distribution in Case 1, in cerebral hemisphere white matter in Cases 2 and 5, and in the region of the lentiform nucleus in Case 6.

Nuclear magnetic resonance imaging (MRI) was also undertaken in 5 of the 6 patients. The distribution of the lesions shown is in Table 6. All 5 patients examined showed periventricular lesions and additional discrete lesions in the central white matter were demonstrated in 4. Case 2 demonstrated lesions restricted to the region of the trigones and occipital horns. The distribution and MRI characteristics of the lesions in these cases are indistinguishable from those observed in 114/116 cases with clinically definite MS without neuropathy (Ormerod *et al.*, 1986) (figs. 3, 4).

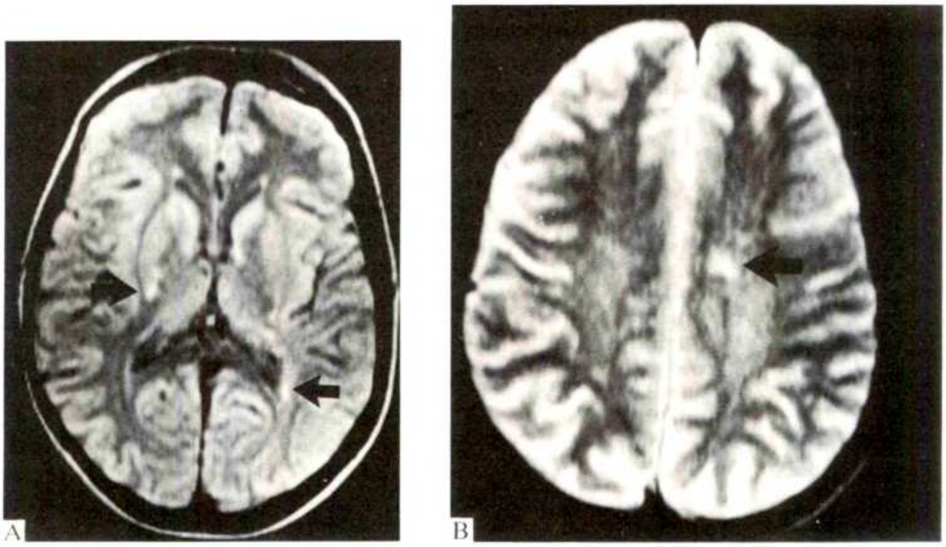

FIG. 3. MR spin echo images from *Case 1*. (A, Tr 2000 ms, Te 60 ms. B, Tr 2000 ms, Te 120 ms.) There are lesions around the trigone of the lateral ventricle (A) and lesions discrete from the ventricle (A, B) which are arrowed.

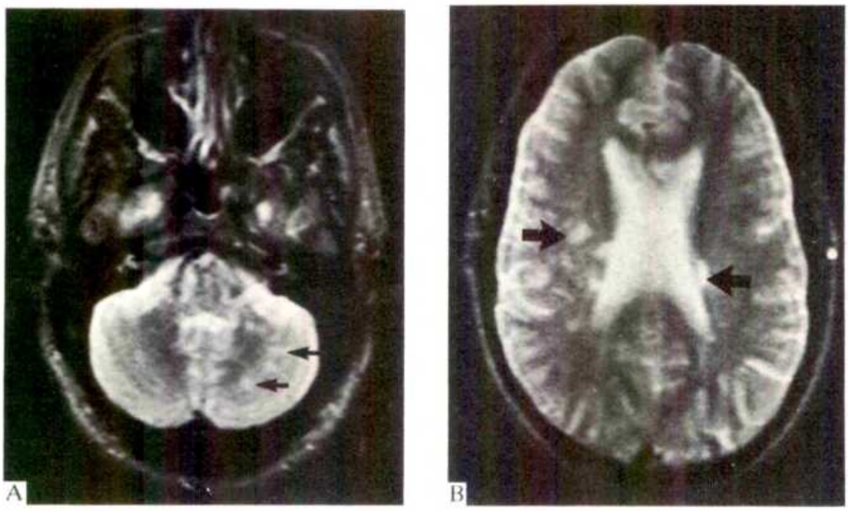

FIG. 4. MR images from *Case 4*. The spin echo images (Tr 2000 ms, Te 120 ms) show lesions in the cerebellar hemisphere (A) and at a higher level (B) lesions are seen around the margins of the lateral ventricles and focally within the cerebral white matter.

TABLE 7. CSF RESULTS

			Protein content		
Case	*Date of examination*	*White cell count (cells/mm³)*	*Total (g/l)*	*% IgG*	*Oligoclonal IgG pattern*
1	Nov. 1968	3	1.45	NA	NA
	Dec. 1969	< 1	1.25	NA	NA
	Jan. 1970	1	0.60	NA	NA
	Apr. 1973	3	1.84	NA	NA
	Feb. 1982	< 1	2.00	10	—
	Dec. 1984	6	2.80	5	—
2	Aug. 1982	1	0.44	6	—
3	Oct. 1981	8	4.28	7	—
	Nov. 1982	3	1.12	5	—
4	Nov. 1981	2	2.50	8	—
5	June 1983	< 1	2.25	NA	+
6	July 1978	7	0.88	17	—
	Nov. 1979	0	1.09	11	—
	Sep. 1983	3	1.73	10	+

+ = present; — = not present; NA = not available.

Cerebrospinal Fluid

The results of CSF analyses, obtained by lumbar puncture, are given in Table 7. A slightly increased mononuclear cell count was obtained on one occasion each in Cases 1, 3 and 6. The total protein concentration was elevated in all patients except for a borderline increase in Case 2 in whom only a single lumbar puncture was performed. The values were usually markedly increased. An oligoclonal IgG pattern was only obtained in two instances (Cases 5 and 6).

Nerve Biopsy

A sural nerve fascicular biopsy was obtained under local anaesthetic from a site posterior to the lateral malleolus in all of the patients. In Case 1, two biopsies were obtained with an interval of 17 years between them. The specimens were processed for light and electron microscopy. Immunohistochemical studies (Dr S. Leibowitz) were undertaken in Cases 1 (second biopsy), 3, 4, 5 and 6.

Methods. The nerves were fixed for 3 h at 4° C in 3% glutaraldehyde in PIPES buffer (pH 7.4) with the addition of 2% sucrose and 1½% potassium ferricyanide. After fixation they were washed for 1 h overnight in the same buffer as used for primary fixation and then further fixed for 3 h at 4° C in 1% osmium tetroxide in the appropriate buffer. The first biopsy from Case 1 was fixed only in 1% OsO_4 in veronal acetate buffer. That from Case 6 was fixed in 3% glutaraldehyde in 0.05 M cacodylate buffer. After dehydration in increasing concentrations of ethanol, the specimens were embedded in Araldite using 1,2 epoxypropane as an intermediary. Semithin sections (1 μm) for light microscopy were stained with thionin and acridine orange (Sievers, 1971) or toluidine blue. Silver sections for electron microscopy were stained with 12.5% (or 25%, Case 6) methanolic uranyl acetate and lead citrate. Myelinated fibre diameters and densities were measured with Kontron image analysis systems either interfaced to a Leitz Ultraphot or from photographs. Unmyelinated axon diameters and densities were obtained from electron micrograph montages. Single fibre preparations were prepared by teasing in Araldite, employing the method described by Spencer and Thomas (1970).

Results. In comparison with control values (Jacobs and Love, 1985), myelinated nerve fibre density was reduced in all the biopsies (Table 8). This was particularly obvious for fibres of larger diameter. Normally 28.7 ± 5.9 (SD)% of myelinated fibres are greater than 8 μm in diameter (Behse *et al.*, 1972). In all specimens, many of the surviving fibres possessed inappropriately thin myelin sheaths for axon diameter, suggesting remyelination. The presence of segmental demyelination was

TABLE 8. SURAL NERVE FIBRE DENSITY*

	Myelinated fibres			
Case	*< 7 μm*	*> 7 μm*	*Total*	*Unmyelinated fibres*
1	1979	1361	3340	52823
	184	86	270	33636
2	1060	48	1108	26666
3	4626	1222	5848	38074
4	1087	473	1560	29757
5	3455	1093	4548	39932
6	960	260	1220	35700
Controls (range)**			7500–10000	30000–40000

* per mm^2. ** Jacobs and Love (1985).

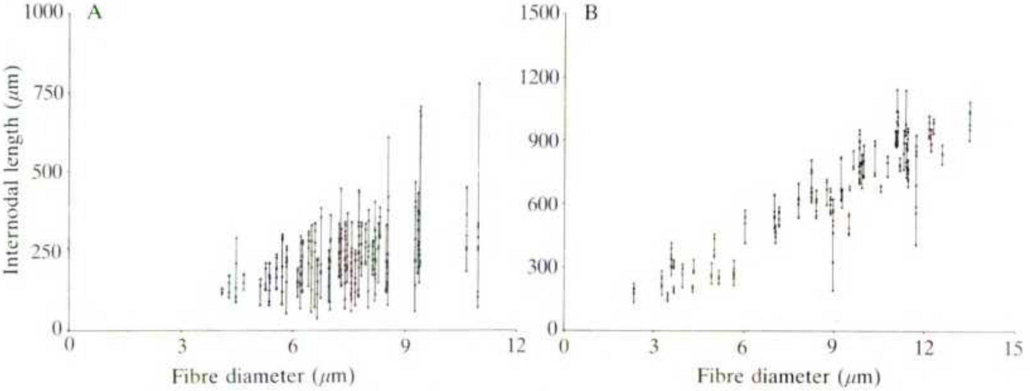

FIG. 5. Relationship between internodal length and fibre diameter for sural nerve. The lengths of internodes on individual myelinated fibres have been plotted against the diameter of the widest internode and the points joined by a vertical line (Fullerton *et al.*, 1965). A, *Case 6*; B, control subject aged 36 years. Considerably greater variability is present for the patient, with many fibres showing both internodes of normal length and short remyelinated segments.

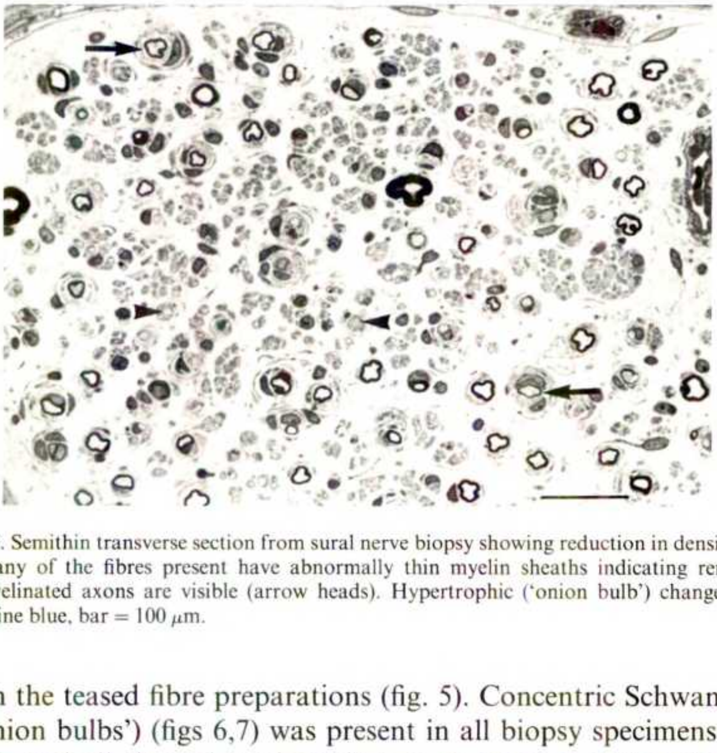

FIG. 6. *Case 6*. Semithin transverse section from sural nerve biopsy showing reduction in density of myelinated nerve fibres. Many of the fibres present have abnormally thin myelin sheaths indicating remyelination and occasional demyelinated axons are visible (arrow heads). Hypertrophic ('onion bulb') change is also evident (arrows). Toluidine blue, bar = 100 μm.

confirmed in the teased fibre preparations (fig. 5). Concentric Schwann cell proliferation ('onion bulbs') (figs 6,7) was present in all biopsy specimens except that from Case 2, and all showed moderately numerous regenerative clusters. Active demyelination was sometimes observed (fig. 7). The density of unmyelinated axons was normal (Table 8). As fascicular biopsies were obtained, endoneurial area could not be assessed, but in all instances the endoneurial spaces were expanded. No

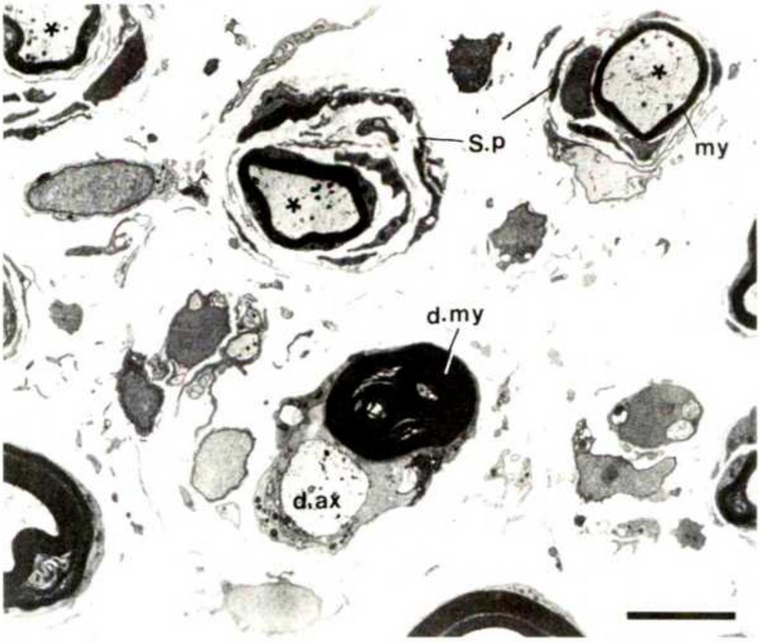

FIG. 7. *Case 3*. Electron micrograph (transverse section) from sural nerve biopsy. One fibre shows a demyelinated axon (*d.ax.*) and myelin debris (*d.my.*) within the cytoplasm of the associated Schwann cell. Other axons (asterisks) have abnormally thin myelin sheaths, indicating remyelination. These fibres are surrounded by proliferated Schwann cell processes (hypertrophic change). S.p. = Schwan cell process, my = myelin. Bar = 5 μm.

inflammatory infiltrates were observed, but occasional mononuclear cells were seen in the endoneurium. Amyloid deposits were not detected and the vasa nervorum appeared normal. No IgG, IgA, IgM or C3 was detected on immunohistochemical staining.

DISCUSSION

Clinical Features

All 6 cases in the present series showed evidence of chronic demyelinating peripheral neuropathy, established by nerve conduction studies and nerve biopsy. Nerve conduction velocity was consistently and severely reduced, and the peripheral nerves were clinically enlarged in 4 of the 6 patients. The CSF protein content was elevated, often substantially, except in one case where there was only a marginal increase. The features were consistent with a diagnosis of chronic idiopathic demyelinating neuropathy.

Other specific identifiable causes for a chronic demyelinating neuropathy of adult onset such a monoclonal gammopathy or inherited metabolic disorder were excluded so far as the investigations permitted. Serum protein electrophoresis was normal in all instances. The leucodystrophies may present in adult life with a combination of peripheral neuropathy and CNS disorder. None of the nerve biopsies showed cellular inclusions of the type encountered in metachromatic leucodystrophy (MLD), Krabbe's disease or adrenoleucodystrophy. Enzyme screening was negative. The reduction in aryl sulphatase A activity in Case 5 was not considered to be significant since, as stated earlier, it did not fall within the homozygote range for MLD. The occurrence of diabetes mellitus in Case 6 is also not likely to be relevant as the neuropathy had become established before diabetes developed. Coincidental adult onset hereditary motor and sensory neuropathy of demyelinating type (type I) is improbable. None of the patients had a family history of neuropathy or displayed associated features such as foot deformity. The magnitude of the elevation of the CSF protein would be inconsistent.

The neuropathy was, in general, of insidious onset and persistent. It was often difficult to apportion symptoms, such as limb weakness or peripheral sensory loss, to a central or peripheral origin. Postural tremor and ataxia may also be a feature both in chronic demyelinating neuropathy and in CNS disorders. The CNS manifestations in these patients were frequently spontaneously relapsing and remitting. In Case 1, there was a phase of marked spontaneous improvement of his neuropathy early in his illness. Improvement in symptoms related to neuropathy occurred in Cases 2, 3 and 4 while receiving treatment. Case 4 was taking azathioprine alone; Cases 2 and 3 were on azathioprine and prednisolone. On the other hand, Case 6 deteriorated progressively while taking azathioprine.

All 6 patients had unequivocal evidence of multifocal CNS lesions. This varied in pattern between cases but included optic neuritis, brainstem involvement such as internuclear ophthalmoplegia, and cerebellar and pyramidal signs. The clinical course was episodic in each.

Confirmation of the presence of CNS lesions was obtained from measurements of central conduction times, cranial CT scans and MRI. The distribution of abnormalities in the latter images was similar to that of plaques at necropsy (*see* Lumsden, 1970). Stewart *et al.* (1984) have shown that satisfactory MR images can be obtained from fixed post-mortem brain. In a study of 6 brains from patients dying with MS it has been possible to identify lesions typical of the disease in the cerebral hemispheres which corresponded in location with similarly shaped abnormal MR images (I. E. C. Ormerod, F. Scaravilli and W. I. McDonald, unpublished). The lesions in the present patients cannot, however, be identified with certainty as being truly demyelinating in nature since indistinguishable appearances can be found in patients with vascular lesions in which degeneration as opposed to demyelination of nerve fibres predominates (Ormerod *et al.*, 1984). It seems likely that the similarity in the images is due to the gliosis which is characteristic of both types of lesion, the alteration in signal being attributable to change in the amount and macromolecular environment of tissue water as a result of the replacement of myelin by astrocytic processes (McDonald, 1986). Nevertheless, despite the lack of specificity of the MR images, in the present clinical context they provide good supporting evidence for the presence of multifocal CNS demyelination.

The clinical features of the CNS disorder in all cases fulfilled the criteria of Poser *et al.* (1983) for the diagnosis of clinically definite MS, although an oligoclonal IgG pattern in the CSF was present in only 2 of the 6 cases (Table 7). In none was the diagnosis confirmed pathologically. The clinical spectrum of MS is wide, embracing relapsing and remitting cases, cases progressive from onset, an acute form (the Marburg type) and the optic/spinal form sometimes referred to as Devic's disease. These syndromes have overlapping clinical pictures. Whether any is aetiologically or pathogenetically distinct from any other is unknown.

The question of a chance association between MS and neuropathy in our cases has to be entertained but seems improbable. MS is relatively common in southern England with a probable prevalence of the order of 75/100,000; chronic inflammatory neuropathy is rare, although precise figures for its prevalence are not available. Moreover, the neuropathy and the CNS disorder developed at about the same time, favouring a common aetiological and/or pathogenetic mechanism. It is of interest that, similar to MS, cases of chronic idiopathic demyelinating neuropathy (CIDP) with a relapsing/remitting course tend to have an early onset, those beginning later tending to pursue a chronic progressive course. In a recent study on CIDP, those with a relapsing course ($n = 60$) had a mean age of onset of 26.8 years, SD 16.0, whereas in those with a progressive course ($n = 32$) it was 51.4 ± 17.7 years (McLeod, 1986).

Peripheral Nerve Abnormalities in Multiple Sclerosis

As stated in the Introduction, demyelinating lesions have occasionally been reported in the peripheral nervous system in MS, mainly in 'acute' MS (Marburg, 1906; Pette, 1928). These lesions are rare in chronic MS (Jellinger, 1969). Pollock *et al.* (1977) have reported evidence of chronic demyelination and remyelination in nerve biopsies from patients with MS, unassociated with inflammatory infiltrates. In chronic neurological disorders the significance of such changes is difficult to assess because of complicating secondary factors, for example focal pressure lesions. The tendon reflexes may be depressed in advanced MS, but in such cases nerve conduction is usually found to be normal (personal observations). Most reports of PNS demyelination in MS have described abnormalities in the spinal roots in the form of focal demyelination, hypertrophic changes (concentric Schwann cell proliferation) and inflammatory infiltrates (Dinkler, 1904; Schob, 1923; Ketelaer *et al.*, 1966; van Gehuchten, 1966; Ninfo *et al.*, 1967; Jellinger, 1969; Schoene *et al.*, 1977; Rosenberg and Bourdette, 1983).

Electrophysiological evidence of peripheral nerve involvement in MS has also been obtained. Hopf and Eysholdt (1978) demonstrated prolongation of the relative refractory period of peripheral nerve fibres. Weir *et al.* (1979) reported increased EMG jitter, and motor unit potential abnormalities were found by the same authors (Weir *et al.*, 1980). Conventional nerve conduction studies have yielded normal results (Gilliatt *et al.*, 1961; Taraschi and Lanzi, 1962; Conrad and Bechinger, 1969; Ginzburg *et al.*, 1971).

The most striking example of peripheral nerve involvement in association with

MS is the single case reported by Lassmann *et al.* (1981*a*). This consisted of a subacutely evolving neurological disorder in a woman aged 26 years with a time course of three months between onset and death. Clinically she displayed an 'organic brain syndrome', brainstem and cerebellar signs, a spastic paraparesis, and muscle wasting in the limbs. Motor nerve conduction velocities were modestly reduced. Death resulted from pulmonary embolism. Autopsy showed recent demyelinating plaques in the CNS and evidence of an inflammatory demyelinating polyradiculopathy. The latter was manifested by demyelination affecting spinal roots (peripheral, Schwann cell-associated portions), especially in the cervical region, which showed inflammatory infiltration and stripping of myelin by macrophages. As mentioned in the Introduction, Ro *et al.* (1983) found hypertrophic changes, indicative of a chronic demyelinating neuropathy, in a sural nerve biopsy from a patient diagnosed on clinical grounds as MS who developed evidence of a distal sensory neuropathy. Best (1985) reported a fatal case of acute polyradiculoneuritis who at autopsy showed multiple recent demyelinated lesions resembling those of MS.

Animal Models of Combined PNS/CNS Demyelination

Experimental allergic neuritis (EAN) is an autoimmune disorder that can be induced in animals by the inoculation of peripheral nerve antigens combined with Freund's complete adjuvant (Waksman and Adams, 1955). Pathologically, this disorder is characterized by multifocal perivascular inflammatory infiltrates associated with demyelination. Both active stripping of myelin off the axon by macrophages and vesicular disintegration of myelin occurs (Ballin and Thomas, 1969; Lampert, 1969). The pattern of disease is influenced by age, species and type of antigen. In the Lewis rat, an acute monophasic illness occurs in older animals, whereas young animals develop a spontaneously relapsing course (J. V. Brosnan, unpublished results). In outbred guinea pigs, Pollard *et al.* (1975) found that the majority of animals developed an acute monophasic illness but that a small proportion displayed a relapsing or chronic progressive course, or relapsed if rechallenged with antigen. Relapsing disease has also been produced in rabbits by multiple injections of antigen (Sherwin, 1966).

In Lewis rats, the lesions are largely confined to the PNS and occur particularly in the spinal roots. In guinea pigs, the peripheral nerves are more diffusely affected and CNS lesions also occur, as they may in rabbits. Extensive studies have not been performed on CNS lesions in animals with relapsing or chronic progressive disease.

Acute EAN is known to be mediated by T cells (Linington *et al.*, 1984; Brosnan *et al.*, 1987). It can be initiated by myelin P_2 protein (Kadlubowski *et al.*, 1980) but whether other peripheral nerve antigens may do so is not yet established. An antibody-mediated peripheral neuropathy can be induced by hyperimmunization with galactocerebroside (Saida *et al.*, 1979), but this has differing histological features. It is not yet certain which antigen is responsible for chronic relapsing EAN, but it is assumed that it is likely to be the same as for acute EAN, the different clinical behaviour being related to age and species-related factors involved in disease suppression (Brosnan *et al.*, 1987). The histological features are the same as those of the acute disease except for appearances attributable to chronicity, such as hypertrophic changes. The antigen (or antigens) responsible for the CNS lesions in those species that develop them also is not established. Peripheral nerve P_1 protein is similar and possibly identical to CNS myelin basic protein (BP). In some species, sensitization to this protein will produce a disease resembling experimental allergic encephalomyelitis (EAE) (Abramsky *et al.*, 1975). The inoculation of 'PNS' P_2 protein, which is not present in the CNS, into Lewis rats, induces EAN without CNS lesions (Eylar *et al.*, 1980; Hoffman *et al.*, 1980; Kadlubowski *et al.*, 1980). If bovine myelin in complete Freund's adjuvant (CFA) is inoculated into Lewis rats, a pure PNS disease is also produced. Serum from these animals, however, contains antibodies to BP, presumably induced by peripheral P_1 protein (Zweiman *et al.*, 1982). Serum from rats with EAN induced by P_2 protein does not contain anti-BP antibodies (Zweiman *et al.*, 1982). Guinea pigs and rabbits, in contrast to rats, often develop combined PNS and CNS lesions when inoculated with whole peripheral nerve in CFA. Yonezawa *et al.* (1968) found that serum from guinea pigs and rabbits sensitized with peripheral nerve in CFA demyelinated PNS tissue cultures if small amounts of CFA and tubercle bacilli were included in the inoculum, but that with larger amounts, demyelination of both CNS and PNS cultures was produced. Although these results on serum-mediated demyelination and the development of antibodies to PNS antigens are of interest, their relevance to the production of demyelinating lesions in vivo is not clear.

EAE is an acute multifocal demyelinating disorder of the CNS induced by the inoculation of CNS tissue with Freund's adjuvant. The antigen that is mainly responsible is myelin basic protein, but it does not seem to be responsible for the full syndrome. Other antigens such as galactolipids are also important (*see* Raine and Traugott, 1982). Similarly to EAN, there is an overlapping involvement of the CNS and PNS, demyelination also occurring in spinal roots. EAE, in many ways, is the CNS counterpart of EAN, but there are clear differences in disease mechanisms. Thus EAE can be transferred by the injection of sensitized lymphocytes into naive recipient animals (Paterson, 1960), whereas this is difficult for EAN (Brosnan *et al.*, 1984).

Of particular interest in the present context is chronic relapsing EAE (Stone and Lerner, 1965; Wiśniewski and Keith, 1977; Lublin, 1982). It has been well characterized histologically (Lassmann and Wiśniewski, 1978, 1979*a*, *b*; Lassmann *et al.*, 1980, 1981*b*, *c*). Perivenous inflammatory infiltrates occur initially, followed by focal areas of demyelination, and finally by plaque-like lesions with similarities to those of MS in the chronic stage. The demyelination occurs both as a result of myelin stripping by haematogenous macrophages and by vesicular disruption, and probably by less well characterized mechanisms (Seitelberger and Lassmann, 1984). It is of interest that demyelination also occurs in the spinal roots in chronic EAE (Raine *et al.*, 1969; Madrid and Wiśniewski, 1978).

The immunopathology of chronic EAE appears to be complex, to vary between species and with the inoculum used to induce it, and probably to depend upon multiple immunopathogenetic mechanisms directed against multiple CNS antigens (Wiśniewski *et al.*, 1982; Lassmann, 1983; Wiśniewski and Lassmann, 1983). The continuous presence of the challenging antigen is necessary for the standard disease: excision of the site of inoculation after initiation results in a monophasic illness (Tabira *et al.*, 1984). However, a chronic relapsing demyelinating CNS disease can be produced in mice by adoptive transfer of lymphocytes sensitized by myelin basic protein (Mokhtarian *et al.*, 1984), indicating that for this experimental paradigm, the continued presence of antigen is not necessary.

There are clear parallels, both clinical and histopathological, between the events in chronic animal models of EAN and EAE with combined PNS/CNS demyelination. Their further study may illuminate the pathogenesis of the clinical syndrome presented by the series of cases reported in the present study and their relationship to chronic idiopathic demyelinating neuropathy, on the one hand, and MS on the other.

ADDENDUM

Since this paper was submitted, a report has appeared in abstract form (J. R. Mendell, S. Kolkin, J. T. Kissell, K. L. Weiss, D. W. Chakeres and K. Rammohan (1986) *Neurology, Cleveland*, **36**, supplement 1, 255) describing MRI findings in a series of 17 patients with CIDP. Six of the 17 patients had periventricular lesions similar to those of MS; 3 of these had clinical evidence of CNS involvement (optic neuritis and myelopathy).

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RESIDUAL VISION IN A SCOTOMA

A FOLLOW-UP STUDY OF 'FORM' DISCRIMINATION

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SUMMARY

This study is a follow-up of a patient, D.B., who was reported (Weiskrantz *et al.*, 1974) to be able to discriminate between simple visual forms within the scotoma caused by a lesion in calcarine cortex. Among other capacities, he was able to discriminate between lines of different orientation in the frontal plane. Given the reported deficits for form discrimination but a high sensitivity for orientation discrimination in primates without striate cortex, the question arises whether D.B.'s apparent 'form' discrimination arises from an ability to discriminate the orientations of components of the figures. It is shown in the first experiment, by using the optic disc as a control, that his ability to detect stimuli in his scotoma cannot be due to stray light falling upon the intact field. Next, his ability to discriminate orientations is confirmed, and an orientation threshold determined. A range of form discriminations is presented varying in degree of orientation cues of their components. It is confirmed that he can discriminate those forms originally studied, in which such differences are large, but not when orientation cues are small or minimal. Finally, his ability to compare two forms both projected within his scotoma is examined. Even when the components of the two forms have large orientation differences and are highly discriminable when presented successively, D.B. appears to be unable to make a 'same-different' comparison when both are presented simultaneously. The evidence is interpreted against D.B.'s having a residual capacity for form discrimination.

INTRODUCTION

In 1974 a report of a patient, D.B., was published in whom a considerable degree of residual visual capacity could be found in an apparently clinically blind scotoma produced by surgical removal of an angioma in the calcarine cortex of the right occipital lobe (Weiskrantz *et al.*, 1974). As in an earlier report (Pöppel *et al.*, 1973) of other patients, D.B. was found to have some capacity to direct his eyes to where the stimulus had been located in his 'blind' field. But in addition he was also able to point even more accurately to such stimuli, and to discriminate between a variety of stimuli. The demonstration of his capacity depended upon the use of particular methods of testing, usually of a forced-choice kind, rather than on the subject's own verbal report of his visual experience, which was often lacking (a phenomenon sometimes known as 'blindsight'). Since that time D.B.'s residual visual capacities

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have been investigated periodically in a variety of situations (some reviewed in Weiskrantz, 1980), and also a number of other investigators have pursued the question of residual vision in scotomata associated with postgeniculate lesions in patients, using a variety of methods (Torjussen, 1976, 1978; Perenin, 1978; Perenin and Jeannerod, 1978; Barbur *et al.*, 1980; Zihl, 1980; Marcel, 1983; Zihl and Werth, 1984*a*,*b*; Marzi *et al.*, 1986).

Primate research also makes it clear that a substantial degree of residual vision can be found in the complete absence of striate cortex and with consequent degeneration of the lateral geniculate nucleus, thereby demonstrating mediation by one or more of several extrastriate pathways (*see* Weiskrantz, 1972, 1980, for reviews). In the monkey, the residual capacity to detect and locate brief small light flashes within the scotoma caused by a lesion *confined* to striate cortex has been shown to be mediated by the superior colliculus (Mohler and Wurtz, 1977). The precise anatomical basis of such residual vision in man still remains to be elucidated as lesions in man are rarely confined to striate cortex and no histological reconstructions of lesions are available as yet of any of the cases studied. It seems likely from work on primates (Zeki, 1978, 1981; Allman *et al.*, 1981) that several specialized 'visual' areas receiving inputs either from the striate cortex or midbrain are crowded into the occipital lobe. As these areas may well be organized functionally on a 'modular' basis, as Zeki suggests, for particular aspects of visual processing, such as colour, orientation, and spatial location (Warrington, 1985*a*), different spectra of residual functions are likely to emerge in a clinical population depending upon the precise limits of the lesions (Weiskrantz, 1980). It is also known from primate work that little residual function will be found if the lesion includes posterior parietal and temporal lobe neocortex in addition to striate cortex (Pasik and Pasik, 1971).

D.B., however, would appear to be an exception to the findings of residual capacity in both human and primate studies in one respect. He appeared to show excellent form discrimination between patterns such as X vs O. In our first study (Sanders *et al.*, 1974; Weiskrantz *et al.*, 1974) these patterns were flashed into his 'blind' field and, provided the stimuli were larger than about 5° he could, with forced-choice guessing, perform at a high level of success.

Other authors, however, have failed to find convincing evidence of form discrimination among the residual capacities of patients with scotomata resulting from postgeniculate lesions (Perenin and Jeannerod, 1978; Barbur *et al.*, 1980). In animal research, striate cortex lesions have been described as reducing rodents and monkeys to a complete dependence upon 'salience', or the attention-capturing properties of visual events, rather than on form per se, such that the animal can detect but not identify visual stimuli (*see* Luciani, 1884; Cowey, 1961). Humphrey (1970) found that when forms were equated in 'salience' (as inferred from detectability measures), they could no longer be discriminated. However, the results of Schilder *et al.* (1972) cannot easily be explained on that basis: they found the destriated monkeys could discriminate a circle from a triangle, and the discrimination was preserved even with transformations in the size and orientation of the stimuli, manipulations that should have yielded large and conflicting differences in salience. Their study, together with that of Humphrey, also clearly ruled out an earlier hypothesis that forms were discriminated by such animals on the basis of total amount of contour (Weiskrantz, 1963). However, the monkeys in the Schilder *et al.* study were severely impaired in learning the circle/triangle discrimination, requiring about more than ten times the number of trials as unoperated controls, and some animals failed. Thus even this result, while exceptional in the animal literature, nevertheless contrasts with the high levels of performance achieved by D.B. without practice for X vs O.

'Forms', however, may vary along dimensions other than 'detectability', 'salience', or amount of contour ('edginess'). In particular, X and O (and also circle vs triangle) differ in the orientations of their major components. Monkeys without striate cortex have a good sensitivity for discriminating orientation. Pasik and Pasik (1980) found that such a monkey had a threshold of 8° in discriminating a vertical bar from a bar off-vertical (preoperatively it was 1°). In our original study, we also found that D.B. was able to discriminate (by forced-choice) a vertical bar from a diagonal bar. With an orientation difference of 27.5°, D.B. performed almost perfectly. The actual threshold for orientation discrimination was not determined.

The main purpose of the present study was to examine the question of whether D.B.'s 'form' discrimination might be derived from his ability to discriminate orientation of components of the figures. But in the first section of the paper a control experiment is reported that is addressed to the prior question of a possible artefact from diffusion of light from the scotoma into the intact part of the visual field, a possibility that must be excluded before other positive findings can be accepted. The optic disc is used as a comparison with the scotoma surrounding it, and diffusion is shown not to be a viable explanation. In the next section (the order reported here is not chronological), his ability to discriminate orientation in his 'blind' field is confirmed using an improved method, and the measured threshold is reported for orientation discrimination for a given eccentricity in the field. In the third section a number of different form discriminations are examined in terms of a possible dependence upon orientation differences. Finally, if form discrimination by D.B. is secondarily derived from orientation discrimination, limited by a system whose function is the detection of unique events and their spatial disposition, it should be difficult to compare two complex and competing forms presented briefly and simultaneously within the impaired field. The fourth section contains an investigation of this question.

CLINICAL STATUS AND GENERAL METHODS

Extent of Scotoma

In January 1976, D.B.'s field defect was reported by him as having shrunk, and this was confirmed by dynamic and static perimetry. His defect originally was a homonymous hemianopia but with a small crescent of spared amblyopic field in his upper left quadrant (*see* Weiskrantz *et al.*, 1974). In 1976 normal vision returned to part of his upper quadrant previously occupied by the amblyopic crescent, and the field defect (minimal limits conservatively determined with 1° 40′ target, incremental contrast of approximately 2.5 log units) was confined largely to the lower left quadrant (fig. 1). After 1976 all discrimination tests were carried out along a meridian passing through the lower left quadrant, usually 45° off-horizontal. But before 1976 some measurements were on the horizontal meridian. Because of the change in the limits of the defect, we report the date at which each of the tests was performed.

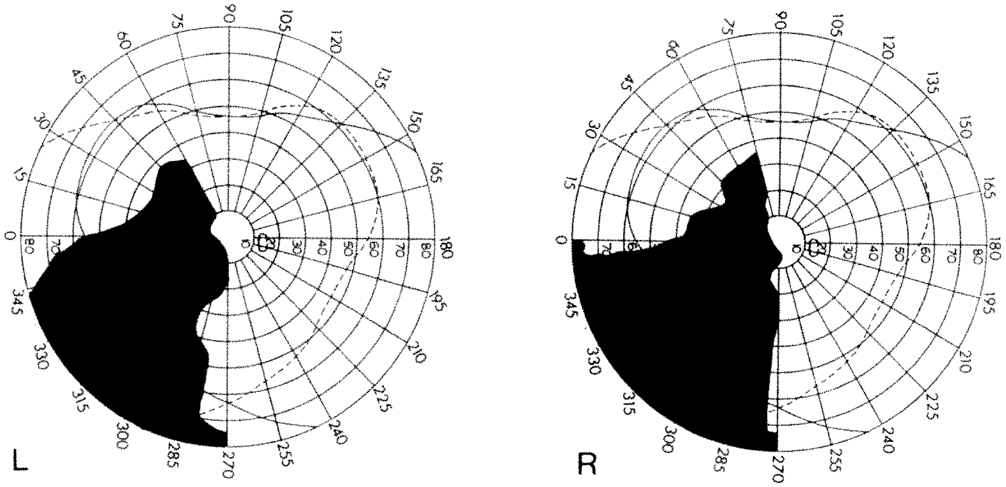

FIG. 1. D.B.'s contracted field defect in 1976, determined with dynamic perimetry in an Aimark apparatus. *See* text for stimulus conditions.

Forced-choice Methodology

In all test series, one of two stimuli was presented in pseudorandom order, and he was required to report which one it was. Typically the presentations were by a tachistoscopic projector into the lower left quadrant of the field, with the other three quadrants independently illuminated and at a higher ambient level than the test quadrant. The light values are given below for each test carried out. He was first shown the stimuli in his good field so that he was familiar with the choice to be made. Usually the duration of the stimuli was set to be less than the saccadic latency. Fixation was well maintained even when the stimulus duration was longer, until *after* his response was made. Knowledge of results was *never* given until the very end of a series of tests, usually lasting several days.

'Awareness'

After each series of trials, D.B. was asked to report his experience. For some stimuli in some regions of the field, D.B. sometimes reported 'feelings' and an awareness of an 'unseen' event. He had developed a sensitivity for reporting fine nuances of his subjective experience. For all the tests with shapes and gratings reported here, except the last section (on matching within the field defect), the stimulus conditions and field position were deliberately chosen and arranged such that he reported that he was *without* any such experience, even with insistent questioning. In all the examples in Sections II and III of the paper, D.B. reported that he was just guessing and had no confidence in his performance. A typical remark would be 'all guess-work; just 50/50'. In the control experiment for diffusion (Section I), he reported having no experience of any stimulus, with one exception for one location to be noted. In the study reported in the last section (Matching), he reported 'bent waves', difficult to describe, and remarked that he felt 'fairly confident. I think I did a little better than 50/50.'

Methods of Stimulus Presentation (*see Tables 2 and 3*)

Aimark perimeter. For the control experiment only (Section I) the smallest size perimeter target was used for the comparisons between the optic disc and the surrounding regions of the scotoma.

Back projection. Black opaque figures were shaped out of solid electrician's tape and fixed on to a transparent glass plate which was illuminated from behind through a uniform diffusing plate, giving the appearance of black figures on a diffusely lit background. D.B. was seated 37 cm from the fixation spot. (The apparatus was the Ives acuity device used in the original study, Weiskrantz *et al.*, 1974, with the spatial frequency of the gratings set very far above the detection cut-off of the normal field.) The apparatus was covered by an opaque card between trials, and a fixation point provided to the side of the apparatus. The stimuli were exposed for 2 s.

Front projection. In another set of tests, the stimuli were projected on to a canvas screen using a Kodak Carousel projector with zoom lens and Forth Instruments tachistoscopic shutter for an exposure of either 125 or 150 ms, as indicated in Table 3. The projector was located behind the subject, at approximately 2.5 m. D.B. was seated 1 m from the fixation spot. The slides were always arranged in spaced positions to eliminate acoustic cues.

Cards. In one test series the stimuli consisted of black drawings on white cards suspended singly on the arm of the Aimark perimeter. Between trials they were covered by white cards. The exposure was 2 s.

OBSERVATIONS

I. *The Natural Blind-spot* (*Optic Disc*) *within the Scotoma as a Control for Diffusion*

Method. The procedure, carried out in April 1982, was as follows (a brief reference to this experiment has appeared elsewhere, *see* Weiskrantz, 1983). We first adjusted the lighting and target parameters so that a target on our own optic discs disappeared completely and without any visible 'halo'. The target was small (33′ in diameter), with a luminance value of 1.15 log ft lamberts, 2 s duration. The luminance of the background was not measured, but was estimated to be −1.0 log ft lamberts. Using these conditions we located the optic disc in D.B.'s *intact* right half-field, with the left eye masked. With forced choice guessing (50% lights, 50% no lights, in pseudorandom order), D.B. performed at chance and reported afterwards never seeing the target. The right eye was then masked, and a mirror-symmetric position in the left field was tested with the same target, as well as two other positions in the first part of the experiment. The order of presentation among the three positions followed a Latin square design, and was as follows: 25°, disc, 10°, disc, 10°, 25°, 10°, 25°, and disc, all along the meridian just below (3°–4°) the horizontal meridian. In each location, 10 trials were given before proceeding to the next location, making a total of 30 trials per location.

Next, we probed three more locations in the scotoma along another meridian, 60° below horizontal, using the same target. Thirty trials each were presented at eccentricities of 45°, 30°, and 15°, in that order.

TABLE 1. PERCENTAGE DETECTION: OPTIC DISC vs OTHER LOCI IN SCOTOMA

	Eccentricity					
			Disc			
	10°	*15°*	*(16°)*	*25°*	*30°*	*45°*
Lower 3°–4° meridian	90%		43.3%	96.7%		
Lower 60° meridian		93.3%			90%	76.7%

Results. D.B.'s percentage correct scores (30 trials per location) are shown in Table 1. When the target fell on the disc, he scored at chance (43.3%). Detection at all other locations was well above chance ($P < 0.01$ by binomial test in each case), and in particular the positions close to the disc were all in the range of 90% or better.

He was questioned carefully after each block of 10 trials. At all locations, except one, he consistently and insistently said that he was 'just guessing.' For example, at the 15° eccentricity, on the lower 60° meridian, he said 'it's a dead area. No sensation. Just guessing.' He said his responses were 'like tossing a coin'. (He made 2 errors out of 30 trials.) The one exceptional location was at 25° eccentricity along the 3°–4° off-horizontal meridian, where he said 'I feel something coming in'.

Thus a target that was not detected when it fell on the natural 'blind-spot' within the scotoma *was* readily detected by D.B. when it fell within the 'blind' scotoma adjacent to the optic disc. Diffusion of light into the intact visual field cannot account for this pattern of findings.

II. *Orientation Discrimination*

The bar orientation discrimination carried out in the original study, while it yielded strongly positive results, had one deficiency, namely that orientation and local field position varied together. Although the differences in field position were not great, nevertheless if there were differences in sensitivity per se, these could be confounded with the supposed orientation discrimination. In the test reported here, this difficulty was circumvented.

Method. The stimuli consisted of a set of square wave gratings (0.9 cycles/deg), each in a circular aperture (10° diameter) projected on to a canvas screen. The grating was either orientated within the aperture with the bars horizontal or rotated off-horizontal by a specified amount, but the position in the visual field of the aperture containing the grating and all other parameters were held constant over the whole set. The centre of the grating was projected at an eccentricity of 45° on the lower left 45° meridian. The fixation distance from D.B. was 1 m. The duration was 150 ms.

The contrast conditions were deliberately set to be weak, with high ambient level. (All light values reported here were measured with an SEI photometer, which is calibrated in log ft lamberts; conversion

TABLE 2. DISCRIMINATION OF HORIZONTAL vs NONHORIZONTAL GRATING

Method	*Year*	*Duration*	*Size*	*Position*	*Contrast*	*Results Orientation difference*
Front projected	1983	150 ms	10° diameter 0.9 cycles/deg	45° on 45°	Light bars = 0.9 log ft lamberts	45° = 95% n = 20
					Dark = 0.68	20° = 85% n = 20
					Ground = 0.60	15° = 82.5% n = 40
					3 Nontest quadrants	10° = 75% n = 20
					= 0.95	5° = 62.5% n = 20

to candles/m^2 can be made by multiplying ft lamberts by 3.4). The value of the light bars within the grating was 0.9 log ft lamberts, and the dark bars 0.68 log ft lamberts, just slightly above the background level of the screen in the test quadrant, 0.60 log ft lamberts. In addition, the three nontest quadrants were flooded independently by projectors such that their ambient level was higher than the light bars of the grating itself (*see* Table 2).

Every trial consisted of presenting either the horizontal or a given non-horizontal grating, and D.B. was required simply to report 'horizontal' 'not horizontal'. The orientation difference was kept constant within groups of 20 trials each, in the order 15°, 15°, 10°, 5°, 20° and 45°.

Results. The results for each orientation difference in terms of percentage correct are given in Table 2. It will be seen that his threshold level (75%, i.e., the value which he discriminates correctly half of the time) is an orientation difference of 10°. Bearing in mind that this is a relatively far eccentric position (45°) and for a briefly flashed stimulus, the sensitivity is highly creditable. Indeed, in his intact right half-field his threshold value for the same stimulus presented at the same eccentricity and for the same duration is also approximately 10°. (The two thresholds cannot be compared exactly because for the good field it had been measured a year earlier and a staircase forced-choice 'titration' method had been used; the contrast was also greater. However, there is no reason to think that any of these differences would have produced a large or significant difference in result.) It is clear from the results that not only is his threshold reasonably sensitive, but he can also achieve a high level of performance at suprathreshold values (95% correct).

III. *'Form' Discriminations*

The discriminations varied from replications of the X vs O, in which the components clearly differ in orientation, to a variety of other discriminations in which orientation cues are diminished or absent altogether. For all discriminations the relevant information about the stimuli is summarized in Tables 3, 4 and 5. The tables show the sizes of the stimuli (height × width) in degrees of visual angle, duration, location in the field and method of presentation. The positions in

TABLE 3. DISCRIMINATION OF X vs O

Method	*Year*	*Duration*	*Size*	*Position*	*Contrast*	*Results*
Back projected	1974/5	2 s	6.5° × 5.5°	20° on 0°	B on W 1.1/2.0 log ft lamberts	92.5% n = 40
Front projected	1976	125 ms	19° × 12°	25° on 35°	W on B not measured	90% n = 30
Front projected	1982	150 ms	9° × 7°	35° on 45°	W on B	85% n = 40
					0.8/0.0	85% n = 48
Front projected	1983	150 ms	10° × 8°	45° on 45°	W on B 0.9/0.6 3 nontest quadrants = 0.95	80% n = 40

W = white; B = black.

TABLE 4. DISCRIMINATION OF T vs 4, X vs TRIANGLE AND STRAIGHT vs CURVED TRIANGLE

Method	*Year*	*Duration*	*Size*	*Position*	*Contrast*	*Results*
				T vs 4		
Back projected	1975	2 s	6.2° × 5°	20° on 0°	B on W 1.0/2.0 log ft lamberts	75% n = 20
				X vs Triangle		
Back projected	1974	2 s	7.7° × 7.7°	18.7° on 0°	B on W 1.0/2.0	48% n = 30
				Straight vs curved triangle		
Printed cards	1975	2 s	17° × 17° × 17°	30°, 45° and 60° on 0°	B on W 0.0/0.6	58% n = 120
Front projected	1982	150 ms	12° × 12° × 12°	45° on 45°	W on B 0.8/−1.1	50% n = 30

B = black; W = white.

TABLE 5. SQUARES vs RECTANGLES AND DIAMOND

Method	*Year*	*Duration*	*Size*	*Position*	*Contrast*	*Results*
Front projected	1983	150 ms	Square and diamond 7.3° × 7.3°	45° on 45°	W on B 0.9/0.6 log ft lamberts	Square vs diamond = 87.5% n = 40
			Rectangle 4.4° × 12.2°			Square vs rectangle = 60% n = 40
Front projected	1983	150 ms	Square and diamond 7.3° × 7.3°	45° on 45°	W on B	Square vs diamond = 95% n = 40
			Rectangle 4.4° × 12.2°		0.9/0.6	Square vs rectangle = 85% n = 20
			Rectangle 5.1° × 10.4°			Square vs rectangle = 70% n = 40

W = white; B = black.

the left visual field are indicated in terms of degrees of eccentricity from the fixation point on a specified lower left meridian, where horizontal meridian = 0° (i.e., ‘25° on 45°’ means ‘eccentricity of 25° on the meridian 45° below horizontal’). Contrast is indicated in terms of direction (B on W = black on white; W on B = white on black).

Methods. The following discriminations were performed.

1. X vs O (*see* Table 3). A number of replications were carried out of the discrimination reported in our original publication (Weiskrantz *et al*., 1974), with various stimulus parameters. This discrimination is one which contains clear orientation differences between the components of the two discriminanda.

2. T vs 4 (*see* Table 4). There is overlap between the horizontal and vertical components of the two stimuli, but one stimulus and not the other contains a diagonal component.

3. X vs triangle (*see* Table 4). The two stimuli both contain diagonals, but one contains in addition a horizontal component.

4. 'Straight' triangle vs 'curved' triangle (Table 4). The stimuli were taken from a graded series of triangles with sides of varying degrees of curvature so as to allow a threshold measure to be obtained, used previously to assess 'form' discrimination in patients with right hemisphere lesions. The discrimination used here was an equilateral triangle vs the triangle in the series with the maximum degree of curvature (No. 7, fig. 2). This was the only discrimination reported here in which stimulus cards were used.

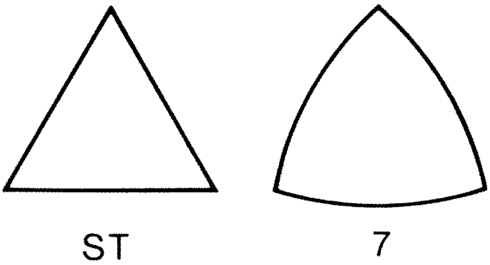

FIG. 2. The 'straight' and 'curved' triangle stimuli.

5. Square vs rectangles vs diamond. Efron (1968) has used a discrimination between a square and a series of rectangles, matched in flux, to study a patient with a putative difficulty in form discrimination. Even though the patient was said to have good acuity, his square vs rectangle discrimination was poor. Warrington (1985*a*, *b*) has used the same approach with other patients with highly comparable results, that is, poor rectangle versus square discrimination. The square and rectangle are matched not only in terms of flux, but also in the orientations of all major components. Therefore, it seemed a useful discrimination to use in the present context.

A graded series of rectangles was prepared, all matched in area (and hence, flux) with the square. Discriminations were carried out between the square and one of the rectangles, using a forced-choice procedure. As a comparison, a discrimination was tested in which the only difference was in orientation, namely a square vs a diamond, that is, with the same square but rotated 45°. A variety of tests were carried out with D.B. using these stimuli, all of which led to a similar conclusion, but here we only report the condition in which, as above, D.B. lacked any acknowledged awareness of the stimuli.

The solid black form, 7.3° × 7.3°, was presented horizontally (square) or diagonally (diamond). The rectangles (*see* below for dimensions) were always presented horizontally. All stimuli were projected at an eccentricity of 45° on the lower 45° meridian, or a horizontally oriented flux-matched rectangle (*see* below for relative dimensions) was projected at an eccentricity of 45° on the lower 45° meridian. The contrast was low, with a moderately high level of ambient illumination with overhead fluorescent lights on continuously (*see* Table 5).

As a preliminary check, D.B. was given 40 trials of X versus O (10° high × 7° wide), and he scored 80% correct (data presented in Table 2). He was then given Square vs Diamond and Square vs Rectangle in an ABBA design, 20 trials per run. The ratio of height to length of the rectangle in this series was 0.36 (see fig. 3).

Another series of trials under identical conditions was later given after additional intervening experience at different eccentricities of fixation. In this later series, a more difficult rectangle was also added, with a ratio of 0.49. He was given the tests in the order Square vs Rectangle (ratio of height to

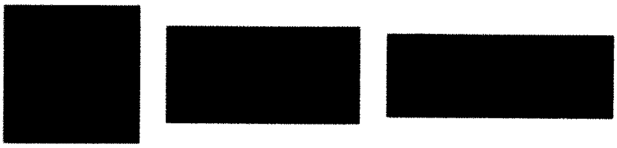

FIG. 3. From left to right: square; rectangle with ratio of height to length of 0.49; and rectangle with ratio of 0.36.

length of 0.36), Square vs Rectangle (ratio of 0.49), Square vs Diamond, Square vs Diamond, and Square vs Rectangle (ratio of 0.49), in that order, 20 trials per block (*see* fig. 3).

Results. Summaries of all results of the 'form' discrimination tests are shown in Tables 3, 4 and 5. It will be seen that the original positive findings with the X vs O were readily confirmed. D.B. consistently performed above chance on this discrimination, even when the luminance differences between figure and background were as low as 0.3 log units.

In all the tests in which orientation differences between the stimuli were present but degraded (Tables 3 and 4), he performed relatively poorly. With T vs 4 he performed at just threshold level, 75%. Using the same method and parameters with the X vs Triangle task, he performed at chance. He was also at chance on the 'straight' vs 'curved' Triangle task, even though this task is well within normal capacity in the intact field, and even though with the projected stimuli a larger contrast level was used than for the successful X vs O discrimination under otherwise similar conditions.

In the first set of Square vs Rectangle and Square vs Diamond tests (Table 5), D.B. scored almost 90% (35/40) on Square vs Diamond, and only 60% (24/40) on the 0.36 rectangle. He showed some improvement in the later set of tests, with an excellent score on Square vs Diamond (38/40) On the Square vs 0.36 Rectangle, he now scored 17/20, and on the Square vs the somewhat more difficult 0.49 Rectangle, he scored 70%.

Thus when orientation was the only cue D.B.'s performance was excellent (and in the absence of any acknowledged subjective experience). For the discriminations with orientation cues relatively degraded, his performance deteriorated, and was never on average above threshold under the conditions tested. When 'shape' was degraded but with orientation of major components matched, in the Square vs Rectangle test, his discrimination broke down, although if the difference in length was great enough he could succeed. As length increases and width decreases, of course, a rectangle approaches first a bar, and finally a line, with an increasingly clear 'horizontal' orientation. This places a limit on this method of testing the hypothesis (together with, of course, an eventual disqualification because of incursion into the intact visual field as the rectangle becomes longer). Therefore, testing could only be carried out for intermediate values of difficulty using Squares vs Rectangles, but within these limits D.B. was deficient when orientation cues were reduced in the Square vs Rectangle series, as compared with Square vs Diamond, where his performance was excellent.

IV. *Matching of 'Forms' within the Impaired Field*

It is easy to discriminate whether two large stimuli such as X and O, placed side by side in a normal visual field, are the 'same' or 'different', even in peripheral vision. On the other hand, if the impaired field is limited to discriminating form secondarily and only indirectly from orientation and directional cues, this task might be considered to be much more difficult to perform, especially if the main function of the extrastriate system is for the detection of unique visual events and their orientation, both with respect to the subject and to their principal disposition in space. Such a detection system would not perform well with competing and complex stimuli, presented simultaneously and briefly. The question was investigated by asking D.B. to make forced-choice 'same'/'different' judgements of pairs of X and O stimuli presented in his impaired field.

Method. It was first necessary to demonstrate that, under the particular conditions of the test, that he could discriminate X vs O. A stimulus was flashed (150 ms) at an eccentricity of 33° from fixation, on the lower 45° meridian in the field defect. The X subtended 9° × 7°, and the O 10° × 8° in visual angle. The luminance difference between the stimulus and ground was small, 0.90 log ft lamberts against 0.60 log ft lamberts. In addition, the three nontested quadrants were independently flooded and had an ambient level of 0.95 log ft lamberts (i.e., higher than the value of the stimulus itself).

D.B. was given two runs of 20 trials each, one run with the stimuli placed such that their nearest point was 5° above the 45° meridian and the second run with it 5° below. He was required to respond 'X' or 'O'.

Then he was given stimuli in both positions simultaneously, one with its nearest point 5° above, the other 5° below the 45° meridian. There were approximately equal numbers of XX, XO, OX, and OO, which were presented in an order constructed from pairs of rows of a Gellerman random sequence table. He responded 'same' or 'different'.

Finally, the same task was carried out in the mirror symmetric position in his good field, and also performed by one of us (E.K.W.).

Results. D.B. had no difficulty in performing the X vs O task when the stimuli were presented singly. He scored 19/20 and 20/20, respectively. But when he had to make a 'same'/'different' judgement for two stimuli presented simultaneously within the impaired field, he performed at chance: 9/20 and 10/20. In his intact field in the mirror-symmetric position, in contrast, he performed perfectly and commented that it was 'easy'. E.K.W. made no errors.

DISCUSSION

Regarding the control experiment for diffusion, the optic disc test is a very stringent one for demonstrating the insufficiency of stray light as an explanation of D.B.'s ability to detect stimuli in his scotoma, as has been suggested (Campion *et al.*, 1983). The maximum spread of discriminable light is 2 1/4°, given the chance performance for the target on the disc. All non-disc positions in the scotoma yielded above chance performance, and all were greater than this distance from the nearest region of intact field. Stoerig *et al.* (1985) have also recently used the optic disc as a control region in a signal-detection analysis of residual vision in a scotoma caused by a postgeniculate lesion, with chance results for detection on the disc and significant if relatively weak levels of detection for the nondisc, independently of large variations in the response criteria of the subject. Their subject, like D.B., reported having 'no sensation whatever, and could hardly believe that his performance was above chance'.

It is important to note that D.B. did not distinguish at all between his lack of experience when the target fell on the genuine blind-spot and when it fell on the four positions that were in the 'dead' field; this was especially apposite for the Latin square design, where the blocks of disc and nondisc trials were intermixed. The importance lies in the comparison having been made directly between the positive residual capacity of the scotoma and that of a region that can objectively be defined as 'blind'. It was only in terms of objective discriminative capacity that the scotoma and the optic disc were different. These results add to other control evidence that make stray light an inadequate explanation, such as the use of high levels of masking light in the intact field (Weiskrantz, 1980), the comparison by several workers of subjects with pregeniculate lesions vs postgeniculate lesions, and analysis of the discriminability of stray light when deliberately permitted (Zihl and Werth, 1984*a*). The question is reviewed in detail elsewhere (Weiskrantz, 1986).

Turning to the main question of this paper, orientation vs 'form' discrimination, when subcomponents of the discriminative stimuli differed in their orientation, as in X vs O, it was repeatedly confirmed that D.B. could achieve high levels of performance. As orientation cues of the components diminished, as in X vs Triangle or in 'curved' vs 'straight' Triangles, so performance deteriorated. Similarly, D.B. performed relatively poorly in discriminating between squares and rectangles, matched in flux, that were within the capacity of normal subjects. Here there are no orientation differences between components. However, when orientation was admitted as the only differential cue, in Square vs Diamond, his performance was excellent. An intermediate example would appear to be T vs 4, which share two orientation components (horizontal and vertical), but differ in the lack of a diagonal component in the T. Here his performance was just at threshold level, 75%.

Independently of these 'form' discrimination tasks, it was found that sensitivity to orientation in the frontal plane was good: the threshold value for discriminating a horizontal from a nonhorizontal grating in the 'blind' field was of the same order of sensitivity as that for the same eccentricity (45°) position in the intact half-field, that is, 10°. In this task all features of the stimuli were absolutely identical except orientation. 10° is, of course, less sensitive a discrimination than is possible when the stimuli are less eccentrically located than in this situation and of longer duration than 150 ms. The value of 10° is of the same order of magnitude as that found for the monkey with total bilateral removal of striate cortex, where the threshold can be as low as 8° (Pasik and Pasik, 1980), although the comparison cannot be made with any precision the animal was free to use whatever part of the field it wished and duration was not limited. But it is clear that striate cortex damage places only a moderate limitation on orientation discrimination in primates.

Given the capacity of the monkey without striate cortex for orientation discrimination, it would not be surprising if it, too, could discriminate X from O, although this has not been tested to our knowledge. However, it has been reported that it can master a discrimination between an array of vertical bars and the same number of bars given random orientations (Keating, cited in Pasik and Pasik, 1980). It might also be understood why such an animal might eventually discriminate a triangle from a circle, as reported by Schilder *et al.*, 1972, although only with very great difficulty.

In the monkey there is good evidence that the superior colliculus is critically involved in the mediation of the *detection* of visual events in the absence of striate cortex (Mohler and Wurtz, 1977). It is not possible to say as yet what pathway might be involved in orientation discrimination. The fact that neurons in the superior colliculus are not sensitive to orientation, as such, unlike those in the striate cortex, does not rule out the involvement of a midbrain pathway. Neurons in the lateral geniculate are also not orientation-sensitive, and so the sensitivity of the striate cortex to orientation must arise from the precise way in which geniculate cells project to striate cortex. Similarly, orientation sensitivity may evolve from the organization in the projection from collicular neurons to their targets, for example, the pulvinar. But other possibilities also exist. For example, the existence has been confirmed in the monkey of an output from the lateral geniculate directly to the *pre*striate cortex (Fries, 1981; Yoshida and Benevento, 1981). Its functional properties are not yet known. Similarly, the properties of the retinopulvinar pathway are not known. But, given that the monkey with confirmed total removal of striate cortex is still capable of good discrimination of orientation, obviously some extrastriate pathways must be able to mediate this capacity. Whatever the route and the mechanism, it seems parsimonious to suggest from the present results that that route cannot also mediate form discrimination in the absence of orientation cues.

A parsimonious interpretation of the present set of findings would reinforce the classical position regarding the necessity of intact striate cortex for 'form' discrimination. It would bring D.B.'s results into line both with the findings with other patients who have residual capacity within the scotomata, where form discrimination is at best only marginal. Perenin (1978), as it happened, like Schilder *et al.* (1972) with the monkey, also used a triangle vs circle discrimination. Only 2 out of their 6 subjects were above chance in this forced-choice discrimination, and only marginally so. For both monkey and human, this particular discrimination appears to be difficult but sometimes possible. On the other hand, not all investigators of human patients have found evidence of good orientation discrimination either. But no others have used a grating stimulus, which may be an especially effective stimulus, as it introduces an obvious spatially repetitive element of redundancy of orientation information. Alternatively, it may be that the lesions in other cases intruded into prestriate cortical regions which may be selectively important for processing of orientation (*see* Cowey, 1979).

The results would fit well with the earlier findings by us of a qualitative difference in sensitivity to 'detection' and 'form' discrimination in the blind field. We found double dissociation between qualitatively different types of visual tasks, depending on whether the intact or the impaired field was used (results of Warrington and Weiskrantz, summarized in Weiskrantz, 1980, 1986). The intact field was superior to the scotoma for form discrimination, under particular conditions when the scotoma was actually superior to the intact field for detection tasks. In those experiments, fortunately as it happened, the 'form' discriminations used stimuli weak in orientation differences (X vs Triangle, and straight vs curved Triangles), which further strengthens the conclusion that D.B. is poor in discriminating forms when orientation cues are not present.

The present findings with D.B. would also fit within the general framework of 'two visual systems' in allowing extrastriate routes a capacity for mediation of detection, location and orientation of a visual event, but requiring integrity of striate cortex (together with other more anterior cortical structures, especially the temporal lobes, to which striate cortex projects over several synapses) for its identification. The evidence from the matching experiment would suggest that the system is biased toward the detection of single unique events, and is stretched by any necessity to compare events. It would be of interest to study the limits of this incapacity with variations in the separation of the stimuli, their properties, together with, say, discriminations of 'one' vs 'two' visual events. The within-field matching experiment was also confounded by D.B.'s reported experience of curious 'waves', and indeed it was this that led us to try to eliminate any such intrusions in experiments in Sections I and II. It is noteworthy, in passing, that he reported that he was 'fairly confident' in the matching experiment, although he performed at chance; in contrast he reported that he had no experience, for example, 'it was pure guess-work—just doing 50/50' in those experiments of Sections I and II in which he performed excellently. This is further evidence for the disjunction between reported subjective experience and actual performance within the realm of residual capacity of the scotoma.

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THE DIAGNOSIS AND MANAGEMENT OF CEREBRAL EMBOLISM AND HAEMORRHAGIC INFARCTION WITH SEQUENTIAL COMPUTERIZED CRANIAL TOMOGRAPHY

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SUMMARY

Haemorrhagic infarction is typically not present immediately after cerebral embolism. Spontaneous haemorrhagic transformation evolves over several days. As a consequence, delayed CT scans are essential to exclude haemorrhagic infarction before initiating anticoagulant therapy. Sequential CT scanning can also help in the diagnosis of cerebral embolism in patients with stroke of unknown cause. In such cases the detection of haemorrhagic infarction on a delayed scan suggests an embolic mechanism. The evolution of haemorrhagic infarction on sequential CT scans graphically demonstrates the dynamic nature of this lesion and thereby indicates why serious brain haemorrhage may result from anticoagulation immediately after cerebral embolism.

INTRODUCTION

Haemorrhagic infarction is an area of ischaemic brain injury in which a large part of the necrotic tissue has become stippled with small haemorrhages. Sometimes these small haemorrhages are confluent; they are usually confined to grey matter. Autopsy study has shown that almost all haemorrhagic infarction is due to cerebral embolism and that over 50% of all embolic infarcts are haemorrhagic (Fisher and Adams, 1951). Haemorrhagic infarction should be distinguished from brain infarction without a haemorrhagic component (anaemic infarction), from frank cerebral haemorrhage without prior infarction and from frank haemorrhage into an embolic infarct in the setting of anticoagulation (Shields *et al.*, 1984). The haemorrhagic element in large cerebral infarctions may often be detected by CT

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TABLE. HAEMORRHAGIC INFARCTION AFTER CEREBRAL EMBOLISM

Case	*Age (yrs)*	*Sex*	*Distribution*[2] *of stroke*	*Cardiac source*	*CT cranial scans*[1]			*Clinical features*[3]
					First	*Second*	*Third*	
1	50	F	RMCA	Cardiomyopathy	Anaemic infarct (day 1)	Haemorrhagic infarct (day 14)	—	E, M
2	79	F	LPCA	Atrial fibrillation	Anaemic infarct (day 3)	Haemorrhagic infarct (day 9)	Resolution of haemorrhage (day 17)	E
3	65	F	RMCA	Atrial fibrillation	Anaemic infarct (day 1)	Anaemic infarct (day 7)	Haemorrhagic infarct (day 21)	E
4	56	F	LMCA	Cardiomyopathy	Anaemic infarct (day 4)	Haemorrhagic infarct (day 12)	—	—
5	72	F	LMCA	Atrial fibrillation	Haemorrhagic infarct (day 4)	Resolution of haemorrhage (day 21)	—	—
6	83	M	LMCA	Atrial fibrillation	Anaemic infarct (day 1)	Haemorrhagic infarct (day 7)	Resolution of haemorrhage (day 24)	—

[1] Day 1 is the day of the stroke. [2] RMCA = right middle cerebral artery; LMCA = left middle cerebral artery; LPCA = left posterior cerebral artery. [3] E = typical embolic temporal profile, i.e., sudden onset of stroke in wakefulness with a maximal deficit at the very beginning of the event. M = multiple strokes.

scans obtained in the initial days after cerebral embolism. Although such cases have been included in the reports of others (Cronqvist *et al.*, 1975; Inoue *et al.*, 1980; Goldberg, 1983; Hakim *et al.*, 1983; Cerebral Embolism Study Group, 1984), there has been little emphasis on the importance of this phenomenon as it relates to the diagnosis and management of cerebral embolism. For this reason we are reporting 6 patients with cerebral embolism of cardiac origin in whom sequential CT scans disclosed delayed haemorrhagic transformation. In these patients the detection of haemorrhagic infarction on delayed CT scans guided decisions regarding timing of anticoagulation treatment and aided in the diagnosis of cerebral embolism.

CASE REPORTS

Case 1

A 50-year-old woman came to hospital with the acute onset of left hemiparesis and right gaze preference. Her previous medical history included alcoholism, cardiomyopathy, and cerebral embolism resulting in occipital infarction four months earlier. CT scan of the brain showed a large area of lucency in the distribution of the right middle cerebral artery (fig. 1A). Anticoagulation was withheld. Repeat CT scan two weeks later showed haemorrhagic areas within the right hemisphere infarct (fig. 1B). The patient was neurologically stable at this time. This finding of haemorrhagic infarction resulted in a further delay of anticoagulation and possibly averted massive haemorrhage into the infarct.

Case 2

This 79-year-old woman was admitted to hospital following the acute onset of a right homonymous hemianopia 48 h before. She had a history of diabetes mellitus, hypertension and chronic atrial

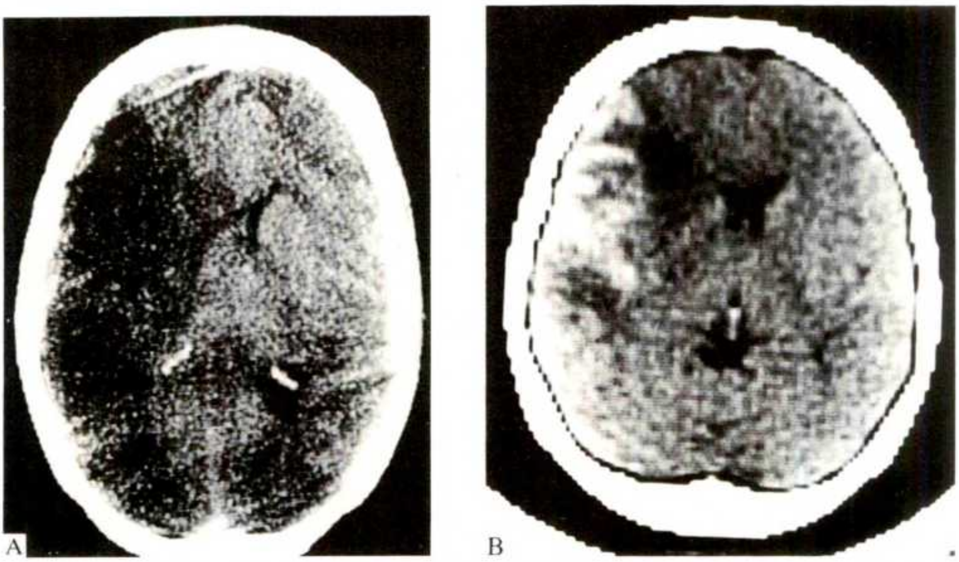

FIG. 1. *Case 1*. A, unenhanced CT scan showing a large right hemisphere infarct on the day of the stroke. B, repeat unenhanced CT scan 2 weeks later showing haemorrhagic stippling in the infarct.

fibrillation. A CT head scan showed a left occipital infarct and generalized atrophy (fig. 2A). Anticoagulation was withheld. Repeat CT head scan eight days after the onset of the stroke showed a small haematoma at the site of the infarction (fig. 2B). The patient was neurologically stable at this time. The demonstration of haemorrhage in the second scan resulted in a further delay in anticoagulation and possibly averted massive haemorrhage into the infarct. A third CT scan sixteen days after the stroke revealed resolution of the haemorrhage with isodensity replacing the haemorrhage seen on the second scan. Warfarin sodium was prescribed and the patient was discharged on the seventeenth hospital day.

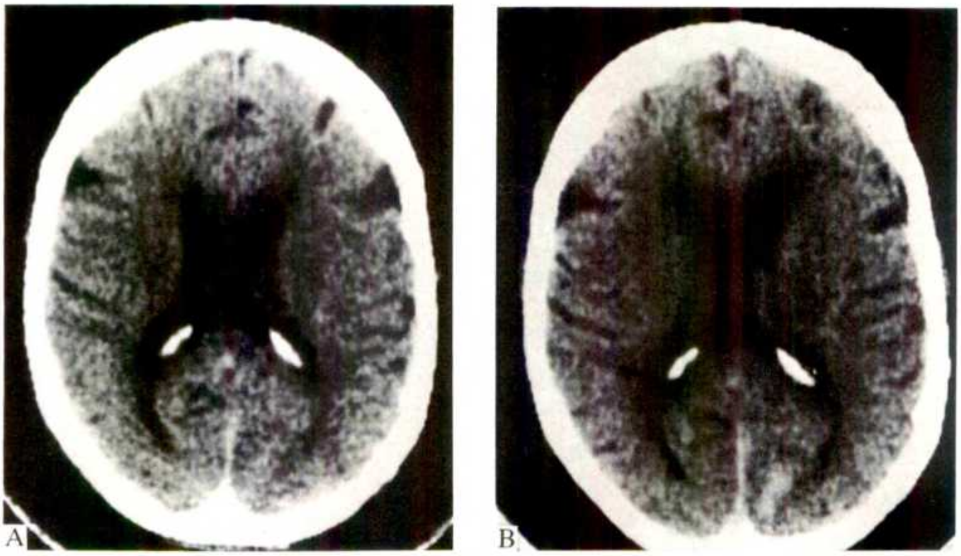

FIG. 2. *Case 2.* A, initial unenhanced CT scan showing infarction in the distribution of the left posterior cerebral artery 48 h after the stroke. B, repeat unenhanced CT scan 6 days later showing an area of haemorrhage in the infarct.

Case 3

This 65-year-old woman was admitted to hospital with the acute onset of a left hemiparesis. She had a right gaze preference and a left homonymous hemianopia. She was diabetic and had chronic atrial fibrillation. CT scan of the brain showed mild atrophy and subtle evidence of infarction in the distribution of the right middle cerebral artery (fig. 3A). Anticoagulation was deferred. A repeat CT head scan six days later showed massive infarction in the right middle cerebral artery distribution (fig. 3B). Anticoagulants were withheld. The left hemiparesis slowly improved. A repeat CT scan twenty days after the stroke showed multiple areas of petechial haemorrhage in the infarct. This patient with definite cerebral embolic infarction illustrates the fact that haemorrhagic transformation of an infarction may develop as late as one week after the stroke.

Case 4

This 56-year-old woman was found by her husband to be speaking incoherently. She had a history of mild hypertension, alcoholic cardiomyopathy and schizophrenia. At the hospital she was found to have a severe mixed aphasia. CT scan of the brain three days after the onset of symptoms disclosed left temporoparietal infarction. Anticoagulation was deferred. Oculoplethysmography suggested moderate left carotid artery stenosis. A CT scan repeated eight days later showed areas of punctate haemorrhage in the area of the infarction. The patient was neurologically stable at this time. This

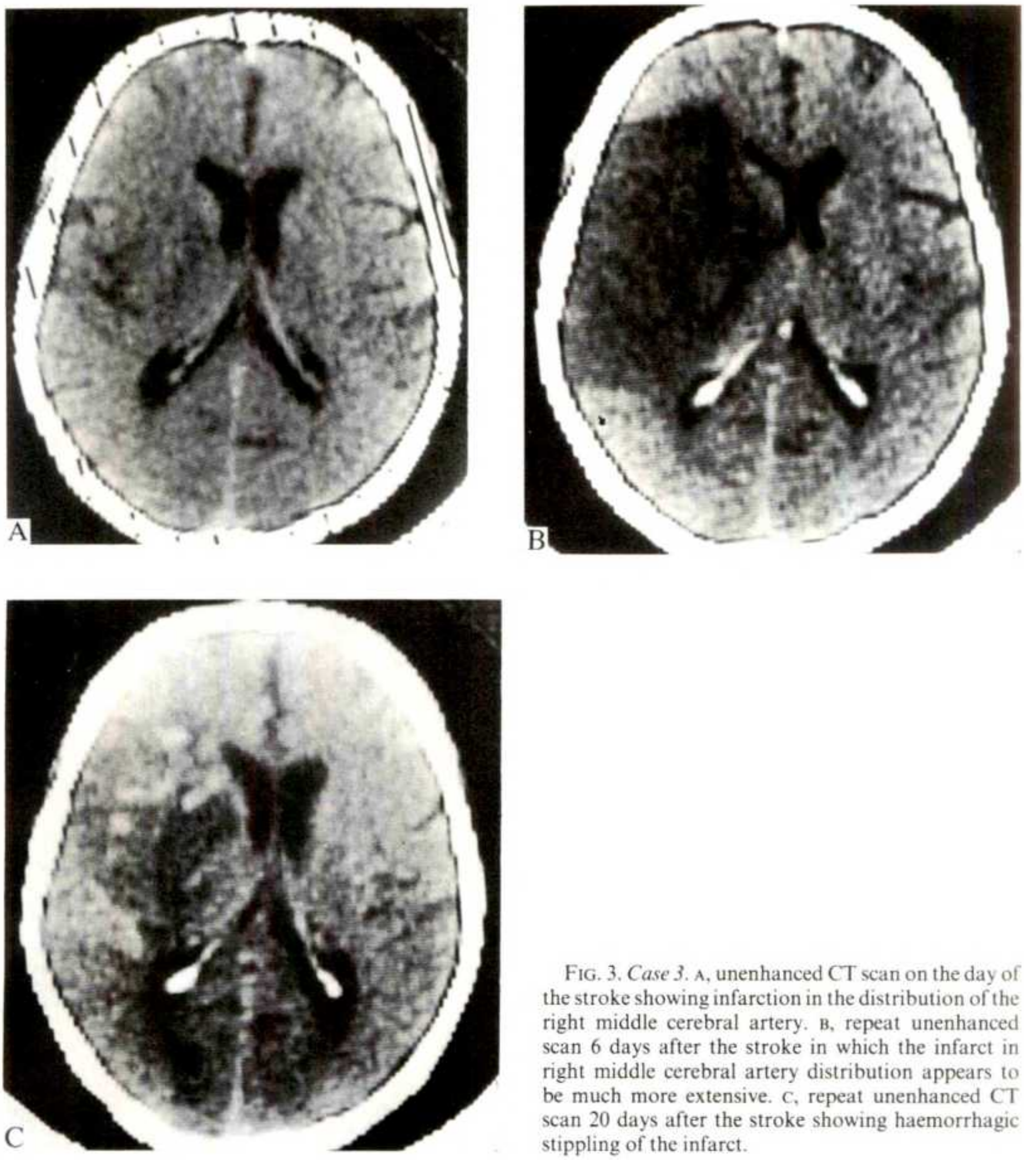

FIG. 3. *Case 3.* A, unenhanced CT scan on the day of the stroke showing infarction in the distribution of the right middle cerebral artery. B, repeat unenhanced scan 6 days after the stroke in which the infarct in right middle cerebral artery distribution appears to be much more extensive. C, repeat unenhanced CT scan 20 days after the stroke showing haemorrhagic stippling of the infarct.

patient demonstrates that an infarct still pale three days after an embolic stroke may appear haemorrhagic on a repeat CT scan eight days later.

Case 5

This 72-year-old woman was found on the floor with aphasia, right homonymous hemianopia and right hemiparesis. She was hypertensive and had atrial fibrillation. A CT scan of the brain without contrast showed a large area of radiolucency in the distribution of the left middle cerebral artery with slight shift of the midline structures to the right. There were areas of haemorrhage within the infarction (fig. 4A). A repeat CT scan seventeen days after admission showed resolution of the haemorrhagic component (fig. 4B). In this case the finding of haemorrhagic infarction on the initial CT scan greatly

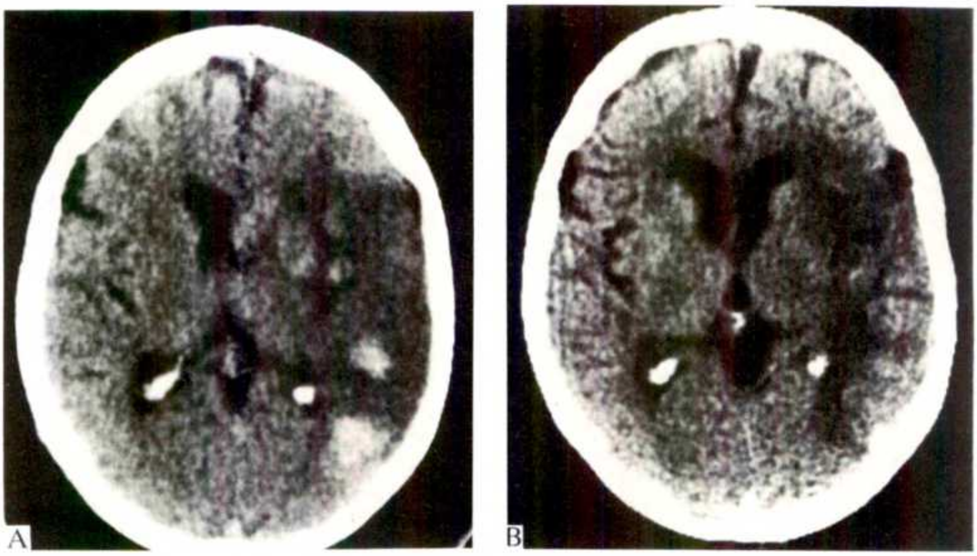

FIG. 4. *Case 5*. A, initial unenhanced CT scan 4 days after the stroke showing a large infarct in the distribution of the left middle cerebral artery in which there are areas of haemorrhage. B, repeat unenhanced CT scan 17 days later revealing resolution of the haemorrhage.

strengthened the diagnosis of cerebral embolism, since the temporal profile of the stroke was uncertain. The presence of haemorrhagic infarction on admission was surprising, because a haemorrhagic component is usually not present immediately after an embolic stroke. This finding was later explained when it was learned that the stroke had probably antedated admission by three days.

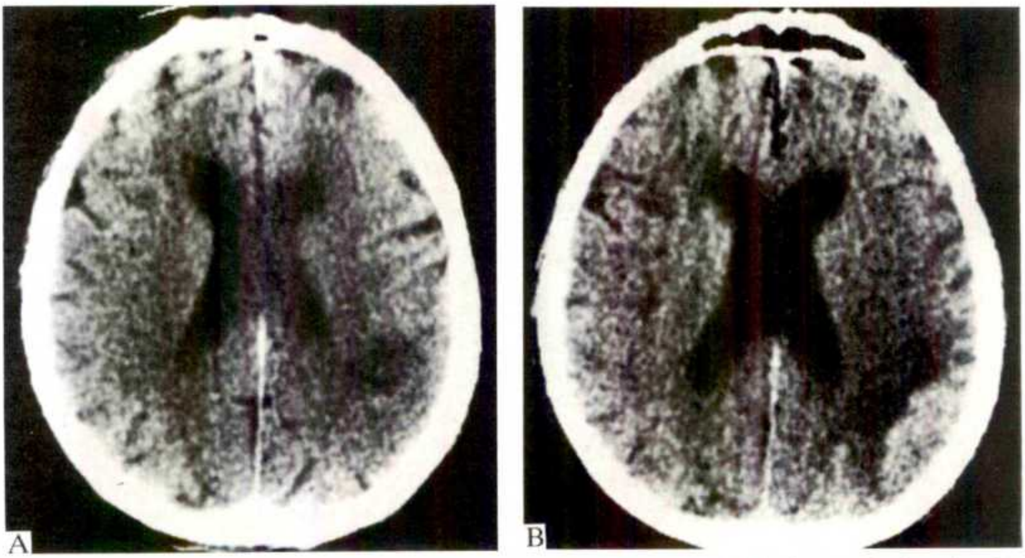

FIG. 5. *Case 6*. A, admission unenhanced CT scan showing left parieto-occipital infarction on the day of stroke. B, repeat unenhanced CT scan 6 days later showing a cortical haemorrhage in the infarct.

Case 6

This 83-year-old man was found on his doorstep where he had fallen after his daily walk. He was aphasic and had a right hemiparesis. He had a history of diabetes, hypertension and congestive heart failure. There was a left carotid bruit. His ECG showed atrial fibrillation. On admission, a CT head scan of the brain showed a left parieto-occipital infarct (fig. 5A). Anticoagulation was deferred. A repeat CT scan six days later showed a lens-shaped area of haemorrhage in the left parieto-occipital infarction (fig. 5B). The patient was improving at this time. A repeat CT scan 23 days after the initial study showed resolution of the haemorrhage; warfarin sodium was prescribed. The appearance of haemorrhage in the infarct on the second scan supported the diagnosis of cerebral embolism in this case in which the temporal profile of the stroke was uncertain.

DISCUSSION

The foregoing patients document the observation that the development of haemorrhagic infarction may be demonstrated with sequential CT scans after cerebral embolism. In each patient, there was a likely cardiac source of embolism and a temporal profile either typical for or consistent with cerebral embolism. In 1 case (Case 5) haemorrhagic infarction was already evident on the initial scan which was not performed until four days after the stroke. In the other 5 cases no haemorrhage was present on the initial CT scan obtained within three days of the stroke, but haemorrhagic infarction appeared on a subsequent scan performed 6 to 20 days after the stroke. In none of these patients was the delayed spontaneous haemorrhagic transformation associated with clinical worsening. These observations indicate that spontaneous haemorrhagic transformation is usually benign. This is in contrast to anticoagulant-related haemorrhage following cerebral embolism which is typically associated with significant neurological deterioration and sometimes death (Shields *et al.*, 1984).

Large infarction size, bleeding disorder and arterial hypertension are not essential for the development of haemorrhagic transformation. Since 3 of these patients had small to moderate-sized infarcts, it is evident that large size is not necessary for haemorrhagic transformation. In each case, prothrombin time, partial thromboplastin time and platelet counts were normal, suggesting that a bleeding disorder is not a factor. One of these 6 patients had unequivocally normal blood pressure throughout the hospitalization. Another with no prior history of hypertension had blood pressure reaching 140/100 mmHg. The 4 other patients had a history of arterial hypertension, but the highest blood pressure measured in these cases was 160/100 mmHg.

The exact incidence of haemorrhagic infarction detectable with CT is uncertain. A recent study estimates a 22% incidence of haemorrhagic change in large embolic infarctions over the first eight days following the stroke (Hakim *et al.*, 1983). It is likely that spontaneous haemorrhagic transformation may develop after the first eight days in some patients, but only a prospective study with sequential CT scans over the initial days and weeks will establish the precise incidence and timing of haemorrhagic transformation. There is no doubt that minimal degrees of petechial haemorrhage are beyond the resolution of the CT scan, and thus mild haemorrhagic infarctions may go undetected. For these reasons, the true incidence of haemorrhagic transformation of large cerebal embolic infarctions certainly exceeds the 22% estimate noted above. This contention is consistent with the higher incidence of haemorrhagic infarction reported at autopsy study of cerebral embolism (Fisher and Adams, 1951).

Mechanism of Haemorrhagic Infarction

Over thirty years ago, Fisher and Adams (1951) reported a high incidence of haemorrhagic infarction in their autopsy study of 123 cases of cerebral embolism. In those cases with anaemic infarction, they usually found an embolus occluding a proximal artery. In those cases with haemorrhagic infarction, there was no embolus occluding a proximal artery. In the latter, however, they often found that there were embolic fragments in distal arterial branches and that the haemorrhagic zone was in the more proximal area of the infarct. From these observations they hypothesized that haemorrhagic transformation occurs when an embolus fragments and migrates distally, thereby opening the previously occluded vessel and exposing necrotic brain to the full force of arterial blood pressure.

Over the past three decades, the correlation of haemorrhagic infarction with cerebral embolism has been strengthened by its production with experimental cerebral embolism in animals (Laurent *et al.*, 1976). In addition, radiological studies in man have supported the Fisher and Adams hypothesis, namely that the reconstitution of blood flow results in haemorrhagic transformation of the embolic infarction. Sequential angiography after embolism has confirmed progressive fragmentation and distal migration of occlusive emboli during the initial days after a stroke (Bladin, 1964; Dalal *et al.*, 1965; Irino *et al.*, 1977*b*). Irino *et al.* (1977*a*) used serial angiograms to correlate the reconstitution of blood flow after arterial occlusion with the appearance of blood in the cerebrospinal fluid. The study of Uemura and Okudera (1977) found haemorrhagic infarction only in those cases of cerebral embolism in which repeat angiography showed reconstitution of flow into the occluded artery. Case 5 of Goto *et al.* (1979) shows the appearance of haemorrhagic infarction in man with angiographic recanalization. Reconstitution of blood flow to an area of cerebral infarction by early endarterectomy has also resulted in haemorrhagic transformation (Bruetman *et al.*, 1963; Wylie *et al.*, 1964; Hass *et al.*, 1966; Caplan *et al.*, 1978). In addition, haemorrhagic infarction has been produced experimentally with reconstitution of blood flow after nonembolic-transient cerebral ischaemia (Kamijyo *et al.*, 1977; Shibata *et al.*, 1978; Koshu *et al.*, 1981).

The cases described in the present paper and others like them graphically demonstrate that haemorrhage into an acute embolic cerebral infarction is a dynamic process. The delayed appearance of the haemorrhagic aspect on sequential scanning, taken with the cumulative clinical and experimental data, confirms the proposal of Fisher and Adams as to the mechanism of haemorrhagic infarction.

Clinical Implications

Sequential CT scanning is an important clinical tool for the diagnosis and management of cerebral embolism. First, serial scans may facilitate the management of a stroke patient in whom no obvious cause or risk factor for cerebral infarction is evident. The physician should consider ordering a repeat CT scan in this situation. Since almost all haemorrhagic infarcts discovered at autopsy are embolic in origin (Fisher and Adams, 1951; Adams and vander Eecken, 1953), the appearance of blood in a previously nonhaemorrhagic infarct strongly suggests an embolic mechanism.

This same principle may also be applied to patients with ischaemic infarction of brain who have evident cardiac disease which may have been the source of embolism. Particularly when the temporal profile of the stroke is unclear (Cases 4, 5, 6), the possibility must be considered that the stroke is due to some cause other than the heart disease. This is especially true in the setting of coexisting large vessel atherosclerosis. For example, Cases 4 and 6 each had a likely cardiac source and evidence of carotid artery disease. Which of the underlying conditions is the cause of cerebral infarction is often unclear in such patients. The development of haemorrhagic transformation on delayed CT scanning in such cases would imply an embolic rather than an atherothrombotic causation. Reaching the diagnosis of cerebral embolism with confidence, in these and other situations, is extremely important as that diagnosis carries with it diagnostic and therapeutic implications.

Sequential scans also may be helpful in deciding the timing of anticoagulation therapy after cerebral embolism of cardiac origin. Patients with cerebal embolism from a persistent cardiac source are usually treated with anticoagulants to reduce the risk of subsequent arterial embolism. However, early anticoagulation after large embolic infarctions of brain can be followed by massive, and at times lethal, haemorrhage into the infarct (Shields *et al.*, 1984). This complication is apparently related to aggravation of spontaneous haemorrhagic transformation by anticoagulant medication. Because of this danger, nearly all authors have recommended delaying anticoagulation after acute cerebral embolism if spontaneous haemorrhagic transformation is documented (Cerebral Embolism Study Group, 1984; Shields *et al.*, 1984). Many authors have suggested that an initial CT scan, obtained within the first 24–48 h after cerebral embolism, is adequate to exclude haemorrhagic infarction before initiating anticoagulation therapy. For example, one study emphasized the view that haemorrhagic transformation most often occurs within 48 h of cerebral embolism (Cerebal Embolism Study Group, 1984). Cases 2, 3 and 4 in the present series, however, indicate that a CT scan performed 48 h after cerebral embolism will undoubtedly miss haemorrhagic transformation in some patients. For example, Case 3 demonstrated a bloodless infarct six days after stroke; a repeat scan two weeks later revealed haemorrhagic infarction. Thus scanning over the initial week may fail to show evidence of bleeding into a cerebral infarct simply because the scan is performed before the spontaneous haemorrhagic transformation.

Although sequential scanning is an advance in our clinical approach to cerebral embolism, it by no means removes uncertainty from the treatment of patients with this disorder. The variables to be weighed in considering anticoagulant therapy are: (1) the risk of *early* reembolization to the brain and the severity of such events; (2) the benefit, if any, of *early* anticoagulation in lowering that risk of *early* reembolization; and (3) the risk of *early* anticoagulation transforming an embolic infarct into a frank cerebral haemorrhage with consequent neurological deterioration.

The risk of early reembolization is not known with certainty; it is likely that this risk is dependent upon many variables including the type of cardiac source. There are only two prospective studies of the natural history of cardiogenic cerebral embolism (Cerebral Embolism Study Group, 1983; Lodder and van der Lugt, 1983); in each study, two treatment groups were established, one with immediate anticoagulation and one without. The 17 patients of Lodder and van der Lugt, managed with no anticoagulation or with no anticoagulation for the first five days after stroke, experienced no recurrence of embolism. In the study of the Cerebral Embolism Study Group, 2 of the 21 patients managed without immediate anticoagulation, developed reembolization to the brain within the first week. However, in the subgroup of 14 patients with atrial fibrillation but without valvular disease, none experienced reembolization over the two weeks following the initial stroke. (All of the early reembolization occurred in patients with a left ventricular sources of embolism.) Of the many retrospective studies which are of possible relevance to this issue, many fail to define criteria for cerebral embolism or reembolism. Suffice it to say that there were 40 patients in the experience of Shields *et al.* (1984) in whom there was delayed or no anticoagulation; there was only one instance of reembolization to the CNS over the first week. Calandre *et al.* (1984) reviewed cases of cerebral embolism in patients with rheumatic heart disease and found one instance or reembolization to brain in 25 patients anticoagulated immediately after a stroke; they found no reembolization in 17 cases in whom anticoagulation was withheld. The view of Fisher (1983) was that 'In our experience with atrial fibrillation, a second embolism has not occurred until day 10'. At least for atrial fibrillation, it is clear that no data have established that there is a high risk of major cerebral reembolization in the initial days after a stroke.

There are also no firm data regarding the value of anticoagulation in decreasing the risk of early reembolization. The one randomized prospective study of this issue showed no statistically significant benefit to early acute anticoagulation (Cerebral Embolism Study Group, 1983). Thus although it is generally believed that chronic anticoagulation lessens the long-term incidence of reembolization, there is no strong evidence that immediate anticoagulation lessens the risk of cerebral embolism in the initial days after embolic stroke.

What has been unequivocally established is the danger of anticoagulation during the initial days after embolic stroke. It had long been debated whether there is risk of frank haemorrhage into an embolic infarct following immediate anticoagulation of patients with cerebral embolism. The few well-documented cases preceding the era of computerized tomography have been reviewed recently (Shields *et al.*, 1984). With sequential CT scanning, however, it has been established beyond question that an initially bloodless infarct can be converted into massive (at times lethal) cerebral haemorrhage. Following the reports by Shields *et al.* of this phenomenon (Shields *et al.*, 1982, 1984) came similar cases (Bass, 1983; Drake and Shin, 1983; Hakim *et al.*, 1983; Hart *et al.*, 1983; Cerebral Embolism Study Group, 1984). The exact risk of this complication has yet to be defined.

The precise incidence of early reembolization to the brain is thus unknown, as is the benefit of anticoagulation in reducing early recurrent embolism. It is certain, however, that immediate anticoagulation can induce cerebral haemorrhage into acute embolic infarction of brain. Many authors who had advised immediate or very early anticoagulation (Easton and Sherman, 1980; Furlan *et al.*, 1982; Koller, 1982; Yatsu and Mohr, 1982; Hart *et al.*, 1983) have subsequently modified their recommendations (Cerebral Embolism Study Group, 1984; Furlan, 1984). A consensus has emerged that immediate anticoagulation be avoided after acute large embolic brain infarction (Cerebral Embolism Study Group, 1984; Shields *et al.*, 1984).

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PATHOLOGY OF THE OPTIC NERVE AND VISUAL ASSOCIATION AREAS

INFORMATION GIVEN BY THE FLASH AND PATTERN VISUAL EVOKED POTENTIAL, AND THE TEMPORAL AND SPATIAL CONTRAST SENSITIVITY FUNCTION

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SUMMARY

Spatial and temporal contrast sensitivity functions (CSF) were compared with visual evoked potentials (VEP) in two groups of patients with pathology selectively affecting different parts of the visual pathway. These consisted of 10 patients with a selective delay of the pattern VEP due to demyelination of one optic nerve (unilateral optic neuritis) and 11 patients with a selective delay of the flash VEP due to pathology of the visual association areas (primary presenile dementia, or Alzheimer's disease). The results led to the following conclusions.

1. Comparison of the VEP and CSF results indicated that VEP latency was more closely associated with the temporal CSF than the spatial CSF. Pathology of the visual association areas which selectively increased the latency of the flash P2 component also reduced sensitivity at low and medium temporal frequencies. In demyelination of the optic nerve, a highly significant correlation was found between the delay of the pattern reversal VEP and sensitivity at high temporal frequencies.
2. Comparison of the results in these two types of pathology suggests that the pattern VEP and flash P1 component, the spatial CSF, and temporal CSF at high temporal frequencies are all processed in the geniculostriate pathway.
3. The flash P2 component and temporal CSF at low and medium frequencies were affected differently from the other measures. The possibility that these processes are transmitted by nongeniculate pathways is discussed.

INTRODUCTION

The use of the visual evoked potential (VEP) in neuro-ophthalmological diagnosis is well established. Important clinical information can be provided by the VEP to both flash (Harding, 1984) and pattern (Halliday, 1982) stimulation. However, it is still not fully understood how the information the flash and pattern VEPs provide relates

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to the underlying visual system and the results provided by psychophysical measures.

We had the unique opportunity to investigate these relationships by studying the vision of patients with selective lesions of the visual pathway that produced marked increases in the latency of either the flash or the pattern VEP. The first group consisted of 10 patients with a selective delay of the pattern reversal VEP due to unilateral optic neuritis (Wright *et al.*, 1984; Harding and Wright, 1986). The pattern reversal VEP was delayed on stimulation of the affected eye only, indicating that the demyelination was prechiasmal. The flash VEP was within normal limits for the group as a whole. The fact that demyelination affects the pattern VEP more than the flash VEP is well documented (Halliday *et al.*, 1972; Wildberger *et al.*, 1976; Cook and Arden, 1977; Duwaer and Spekreijse, 1978).

The second group consisted of 11 patients with primary presenile dementia showing the unusual combination of a delayed flash VEP (P2 component) and a normal pattern VEP (Wright *et al.*, 1984). Primary dementia of the Alzheimer type is associated with a defect of cholinergic transmission in the brain, including the visual cortex (Perry *et al.*, 1977; Davies, 1979; Rossor *et al.*, 1982), and our group has shown that the unusual combination of a delayed flash and normal pattern VEP in dementia can be reproduced in normals using the centrally acting anticholinergic drug hyoscine hydrobromide (Bajalan *et al.*, 1986). The results suggest that cholinergic mechanisms influence the flash VEP (P2 component) more than the pattern VEP. The pathology in Alzheimer's disease has been shown to affect the occipital areas but spare the primary visual cortex (striate cortex, or Brodmann's area 17 (Brun and Gustafson, 1976; Benson, 1982; Schlotterer *et al.*, 1983). Applying this to our VEP results in dementia, it could be inferred that the pattern VEP reflects the integrity of the primary visual cortex and the flash P2 component the integrity of the higher visual association areas.

Optic neuritis and primary presenile dementia therefore represent the two extremes of the visual pathway—unilateral optic neuritis affecting the optic nerve, producing a selective pattern VEP delay, and dementia affecting the visual association areas of the cortex, producing a selective flash VEP delay. The psychophysical visual defects produced by these abnormalities of the visual pathway were investigated by measurement of spatial and temporal contrast sensitivity functions (CSF) and visual acuity (VA).

MATERIAL AND METHODS

Patients

Ten patients with a unilateral delay of the pattern reversal VEP due to optic neuritis were referred from the Birmingham and Midland Eye Hospital. The time since onset of the symptoms varied from 1 to 90 months and they had all recovered from the acute phase of the condition. The mean age of the group was 37.3 ± 8.6 yrs. The unaffected eyes were used as controls and the results were also compared with those of a control group with an equivalent balance of males and females and a mean age of 38.9 ± 8.5 yrs.

The patients with dementia were referred for a larger study on the effect of dementia on the VEP. The length of time since onset of symptoms varied between 1 and 6 yrs and any treatable causes of the dementia had been excluded. No patient with evidence of ophthalmic pathology was used. The 11 patients included in this study represent those with a delayed flash VEP who were mentally capable of undertaking the psychophysical tests. The mean age of the group was 63.6 ± 5.8 yrs. A normal control group was used consisting of volunteers of an equivalent balance of males and females and a mean age of 62.6 ± 6.3 yrs. A patient control group was also used in an attempt to compensate for complicating psychological factors such as confusion and slowness to respond. They had affective disorders, such as depression, but no clinical evidence of dementia. The mean age of this group was 57.6 ± 7.6 yrs. The patients and patient controls were referred from the Queen Elizabeth and Midland Nerve Hospitals by consultant psychiatrists who determined the diagnoses on clinical symptoms alone.

Electrophysiological Techniques

Signals were recorded from electrodes at 02 and 01, referred to Fz (International 10–20 system of nomenclature). A Grass PS22 stroboscope at Intensity 2 produced a flash of 68 nits twice per s. Patterned stimuli were produced by an optical projector system (Drasdo, 1976) and consisted of back projected checkerboards of 56 and 19 min of arc in a circular field of 28° diameter, and a foveal stimulus of 13 min checks in a 3° diameter field. The contrast of the checks was 0.76 and the mean luminance 1050 cd/m^2. For pattern reversal stimulation the pattern was abruptly moved through the width of one square by an oscillating mirror twice per s. Pattern onset-offset stimulation was produced by a lenticular wheel with a clear sector rotating in front of the projector beam twice per s. The pattern appeared on the screen for 150 ms and was replaced by a grey field of equal mean luminance for the remainder of each cycle.

Psychophysical Methods

Visual acuity was measured on a standard Snellen chart of 0.94 contrast with an ambient luminance of 42 cd/m^2. For statistical analysis the results were converted into decimal notation, with intermediate results for each letter on the line (Drasdo and Haggerty, 1981).

Spatial and temporal contrast sensitivity functions (CSF) were measured using an ascending and descending method of limits (Woodworth and Schlosberg, 1954) and the mean of six readings taken for each threshold value. The ascending and descending method should minimize any effects due to the slowness of response of the psychiatric patients.

The spatial CSF was measured using stationary gratings of sinusoidal luminance profile on an oscilloscope. The mean luminance of the oscilloscope screen was 13.5 cd/m^2 and the contrast of the grating could be varied between 0 and 0.35. The green screen was viewed through a circular aperture in a cardboard surround of approximately equal colour and luminance. Twelve cycles were displayed and this number was kept constant throughout to stimulate a constant number of cortical neurons (Virsu and Rovamo, 1979). Spatial frequency was varied by changing the distance between observer and screen (Hoekstra *et al.*, 1974; Blakemore and Campbell, 1969). The contrast sensitivity function was sampled at three points: 1.3 cycles/deg (9° field), 4 cycles/deg (3° field) and 12 cycles/deg (1° field).

The temporal CSF, or de Lange curve, was measured using a 2° yellow LED source which produced a sinusoidal temporal luminance variation. The frequency and modulation of this sinusoidal flicker could be varied independently, the range of modulation being 0 to 0.30. The temporal CSF was sampled at three points, 3.3 Hz, 10 Hz and 30 Hz. The mean luminance of the flickering source was 40 cd/m^2 and the 68° surround was matched for colour and luminance.

Analysis of Results

The most consistent and significant VEP components in normals are P100 (100 ms) for the pattern reversal VEP, CII (100 ms) for the pattern onset VEP and P1 (70 ms) and P2 (120 ms) for the flash VEP. The components are quantified in terms of latency—time from stimulus onset to peak of component in ms—and amplitude of the signal from the previous peak in μV. The VEP results presented are from the same eye that was used for the psychophysical measures. As there were no significant differences between the hemispheres, the values of the VEPs recorded from 02 and 01 are averaged for clarity.

The psychophysical threshold values are displayed graphically as contrast sensitivity (reciprocal of threshold) on a log/log scale. For statistical comparison of the dementia patients and patient controls, the t test for independent samples was used. The t test for related samples was used for analysis of the optic neuritis results, as the two eyes of the same patient were compared in each case.

RESULTS

Electrophysiology

Optic neuritis. Before using the apparently unaffected eyes as controls in the patients with unilateral optic neuritis we compared their pattern reversal P100 latencies with those of a normal control group of equivalent age and sex. No significant differences were found between the groups, establishing the validity of using the unaffected eyes as controls.

TABLE 1 EFFECT OF OPTIC NEURITIS ON THE LATENCY OF THE VEP

		Affected eye	*Unaffected eye*	*Significance level*
Flash P2		131.5 ms ±17.2	124.8 ms ±12.8	n.s.
Pattern reversal (P100)	56′ check	141.6 ms ±14.8	105.2 ms ±9.1	$P < 0.001$
	19′ check	143.1 ms ±12.8	103.5 ms ±5.5	$P < 0.001$
	13′ check	142.6 ms ±14.0	104.0 ms ±7.3	$P < 0.01$
Pattern onset (CII)	56′ check	137.8 ms ±16.6	102.2 ms ±10.9	$P < 0.001$
	19′ check	144.9 ms ±12.0	105.6 ms ±22.7	$P < 0.01$
	13′ check	146.9 ms ±31.9	120.1 ms ±14.2	$P < 0.01$

Table shows mean values ± 1 SD. n.s. = not significant.

Table 1 shows that optic neuritis produces a mean delay of the pattern onset-offset VEP that is as large as the delay of the reversal VEP. The magnitude of the delay did not vary significantly with check size. The optic neuritis also caused a significant reduction in the amplitude of the pattern reversal P100 evoked by the medium checks and pattern onset CII components evoked by both large and medium checks, but not those evoked by the smallest checks (Table 2). The flash VEP is not significantly affected by the optic neuritis.

TABLE 2 EFFECT OF OPTIC NEURITIS ON THE AMPLITUDE OF THE VEP

		Affected eye	*Unaffected eye*	*Significance level*
Flash P2		6.8 μV ±5.1	8.1 μV ±6.1	n.s.
Pattern reversal (P100)	56′ check	6.2 μV ±3.4	7.7 μV ±3.2	n.s.
	19′ check	4.3 μV ±2.4	7.5 μV ±4.7	$P < 0.01$
	13′ check	3.4 μV ±2.0	3.8 μV ±2.1	n.s.
Pattern onset (CII)	56′ check	5.8 μV ±3.5	7.3 μV ±3.6	$P < 0.05$
	19′ check	5.6 μV ±3.3	8.3 μV ±4.7	$P < 0.05$
	13′ check	5.6 μV ±5.8	6.9 μV ±5.6	n.s.

Table shows mean values ± 1 SD. n.s. = not significant.

TABLE 3 EFFECT OF DEMENTIA ON THE LATENCY OF THE VEP

		Dementia group	*Patient control group*	*Significance level*
Flash P1		81.1 ms ±9.0	73.7 ms ±8.2	n.s.
P2		153.0 ms ±6.6	131.9 ms ±6.4	$P < 0.001$
Pattern reversal (P100)	56′ check	109.4 ms ±7.0	112.4 ms ±10.2	n.s.
	19′ check	114.3 ms ±7.6	113.6 ms ±6.8	n.s.
	13′ check	115.4 ms ±11.7	114.1 ms ±9.0	n.s.
Pattern onset (CII)	56′ check	113.8 ms ±8.5	119.0 ms ±13.4	n.s.
	19′ check	118.1 ms ±20.6	113.3 ms ±14.3	n.s.
	13′ check	134.8 ms ±15.6	121.7 ms ±24.5	n.s.

Table shows mean values ± 1 SD. n.s. = not significant.

Dementia. The VEP latency results from the dementia group are shown in Table 3. Despite the marked delay of the flash P2 component, no other flash or pattern VEP component is significantly affected. The dementia does not affect the amplitude of the flash VEP components, nor the pattern reversal or onset VEP components at any check size.

Psychophysics

Optic neuritis. The visual acuity of the affected eye of the optic neuritis group had returned to 6/6 or better in 8 of the 10 patients and was 6/9 in the other 2. The mean VA of the affected eyes, however, was slightly but significantly worse than that of the unaffected eyes ($P < 0.01$).

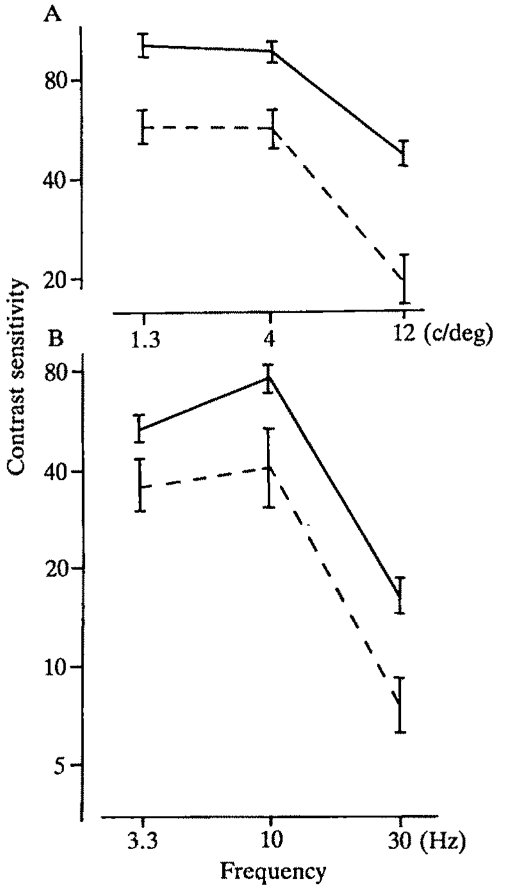
Several patients reported reductions in their perception of contrast and this was confirmed by the pyschophysical results. Eight patients had reduced contrast sensitivity at all three spatial frequencies and the other 2 showed reductions at the medium and high frequencies. The mean values for the group (fig. 1A) show that the contrast sensitivity reduction in the affected eye is highly significant when compared with the unaffected eye at all three spatial frequencies ($P < 0.001$). Similarly, the mean reduction in temporal contrast sensitivity is highly significant ($P < 0.001$) and affects all three temporal frequencies (fig. 1B). Eight of the patients showed reductions at all three temporal frequencies and two at medium and high frequencies only.

Dementia. The most significant psychophysical result was the reduction in temporal contrast sensitivity at low ($P < 0.01$) and medium ($P < 0.05$) temporal frequencies (fig. 2B). There was no significant difference in results between the dementia and patient control groups for the highest temporal frequency, all three spatial frequencies, and visual acuity.

Relationship between Electrophysiological and Psychophysical Measures

The pathology in dementia affects the visual association areas but is not believed to affect visual processing at earlier stages in the visual pathway. The results show that this type of pathology affects the flash P2 component and temporal processing at low and medium temporal frequencies, which suggests that these measures reflect the same mechanisms. Optic neuritis, however, presents a more complicated picture as the major site of the pathology is the optic nerve where luminance and pattern fibres, and those destined for cortical and subcortical routes, are presumed still to run together. It is also possible that the retina is affected. The demyelination has affected the latency and amplitude of the pattern reversal and onset VEP as well as the spatial and temporal CSFs at all frequencies. In an attempt to disentangle these measures and to determine which related most closely to each other, we made use of the fact that we had the ideal control—an unaffected optic nerve connected to the same brain. The results from stimulation of each eye separately effectively show the same individual with and without demyelination. The ratio between the eyes was calculated and correlations between the various measures determined.

The relative spatial CSF defects at low, medium and high frequencies were compared with the relative pattern VEP latency and amplitude defects for the large, medium and small check sizes, respectively. The only significant correlation was



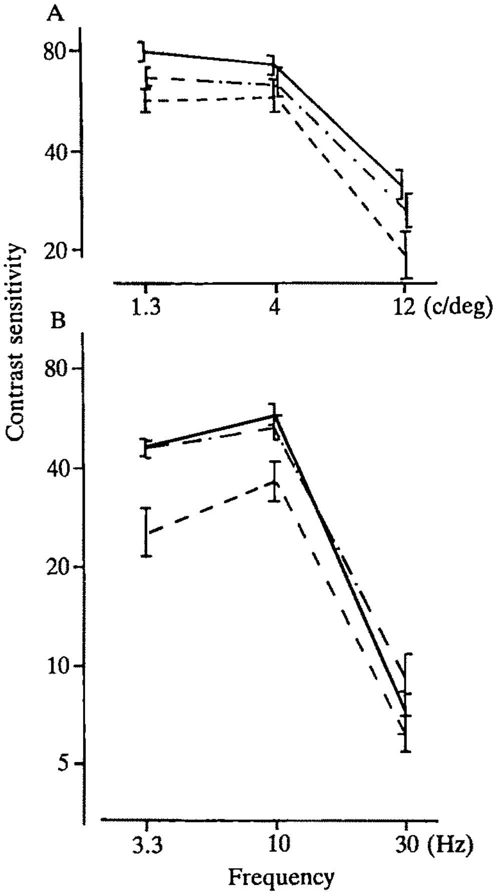


FIG. 1 (*left*). Unilateral optic neuritis: mean values ± 1 SEM from 10 patients. Spatial CSF (A) and temporal CSF (B) are both reduced approximately equally at high, medium and low frequencies Unaffected eye (continuous line), affected eye (broken line).

FIG. 2 (*right*). Primary presenile dementia: mean values ± 1 SEM from 11 patients showing that (A) spatial CSF is not significantly reduced in dementia compared with patient controls, (B) temporal CSF is significantly reduced at low and medium but not at high temporal frequencies. Normal controls (continuous line); patient controls (dashed and dotted line); demented patients (dashed line).

between the relative CSF defect at the highest spatial frequency and one of the only pattern VEP measures that was not significantly affected by the optic neuritis—pattern reversal amplitude for the 13 min check (correlation coefficient 0.61, $P < 0.05$).

The relative temporal CSF defects were compared with the temporal aspect of the pattern VEPs, namely latency. The 3 Hz and 30 Hz results were compared separately, as low and high temporal frequencies are believed to be processed by completely separate systems (Kelly, 1964). A highly significant relationship between temporal contrast sensitivity at the highest frequency (30 Hz) and pattern VEP latency (56 min check) was found. The correlation coefficients were 0.89 for the pattern onset CII component ($P < 0.001$) and 0.71 for the pattern reversal P100 component ($P < 0.02$).

No significant correlations were found between temporal contrast sensitivity at 3 and 30 Hz and the latency of the P100 and CII components evoked by the smallest (13 min) check. Temporal CSF did not show any significant relationship with pattern VEP amplitudes, nor with flash P2 latency.

DISCUSSION

Optic Neuritis

The results show that demyelination in the optic nerve has a marked effect on the fibres transmitting pattern information. This effect does not appear to be confined to X or Y fibre subsystems (Kulikowski and Tolhurst, 1973) but reduces processing at high, medium and low spatial and temporal frequencies approximately equally.

One of the main purposes of our investigation was to see if we could determine how VEP measures relate to visual psychophysics. The results of this study indicate that pattern VEP *latency* and psychophysical sensitivity at high *temporal* frequencies are determined by the same groups of fibres. It was not possible to establish such a clear relationship between spatial psychophysical measures and the VEP, although a correlation was found between spatial contrast sensitivity and the amplitude of the pattern reversal VEP for the smallest stimuli. Other researchers have also been able to relate spatial contrast sensitivity defects to pattern reversal VEP amplitude at high spatial frequencies (Plant, 1983) but not to latency (Bodis-Wollner *et al.*, 1979). Similarly, Halliday *et al.* (1974) showed that the recovery of visual acuity (another spatial measure) after the acute phase of optic neuritis correlated with pattern VEP amplitude but not latency.

Dementia

It has already been stated that the pathology in Alzheimer's disease is believed to spare the primary visual cortex but affect the visual association areas. Our normal pattern reversal and pattern onset-offset VEPs would be consistent with a normally functioning visual pathway up to the primary visual cortex, possibly including both Brodmann's areas 17 or 18 (Blumhardt and Halliday, 1981; Jeffreys and Axford, 1972*a*, *b*).

The origin of the flash P2 component has not been conclusively established but the delay produced by dementia in the presence of a normal pattern VEP has led our group to suggest it originates in the visual association areas (Wright *et al.*, 1984). In man, area 19 is the largest of the three divisions of the occipital lobe (Duke-Elder, 1961) so it is quite probable that P2, the largest component of the flash VEP, is generated in this area. Early researchers suggested that the flash components occurring before 100 ms, including P1, are generated in the primary visual cortex, while the components occurring after 100 ms including P2, are generated in the secondary visual cortex (Ciganek, 1961; Vaughan, 1966). If this is the case, then the flash P1 component should not be affected by the pathology in dementia. Inspection of the results (Table 3) shows that there is a small difference in the mean P1 latency of the dementia and patient control groups but that it is not statistically significant. Previous studies using larger numbers of patients have also found no significant increase in flash P1 latency in dementia (Wright *et al.*, 1984, 1986), indicating that it could be arising from the unaffected primary visual cortex. If this is the generator site, the flash P1 component in normals would not be expected to be as large and well defined as the pattern VEP, as the work of Hubel and Wiesel has shown that the neurons of the primary visual cortex give an optimal response to patterned stimuli (Hubel, 1982). Normative studies (Wright *et al.*, 1985) confirm that this is the case. They also show that the flash P2 component is much more affected by the normal ageing process than the flash P1 or pattern reversal components, which indicates that our results in dementia are like an exaggerated ageing response.

The selective distribution of the pathology and of the VEP abnormalities in dementia give a fascinating model for comparison with visual psychophysical results. Once again, the most interesting psychophysical results were those provided by measurement of the temporal CSF. The patients with dementia showed a reduction at low and medium but not high temporal frequencies. This relates well to the flash VEP results—the faster positive component, P1, and the psychophysical high temporal frequency response are unaffected while the slower positive component, P2, and the low and medium frequency responses are affected by the pathology. Pattern VEP latency and high temporal frequency processing were both normal, which would be consistent with our previous suggestion that they are determined by the same mechanisms.

The normal spatial contrast sensitivity found in our dementia study is consistent with the results of Schlotterer *et al.* (1983) who concluded that the primary visual cortex was unaffected by the pathology in dementia. Nissen *et al.* (1985), however, reported an apparent reduction in spatial contrast sensitivity in demented patients when compared with normal controls. Fig. 2A shows that both our patient groups have a lower contrast sensitivity than the normals, but our results using the patient controls confirm that there is no significant reduction in contrast sensitivity attributable to the dementing process itself.

Where in the Visual System are these Visual Processes Determined?

In discussing the implication of our findings, the results from the optic neuritis and dementia groups, when taken together, lead us to suggest that high temporal frequency processing and pattern VEP latency are determined by a common mechanism in the geniculostriate pathway. The primary (or striate) visual cortex is probably also the processing area for the spatial CSF and the flash P1 component. Our results indicate, however, that the flash P2 component and low and medium temporal frequencies have different characteristics and are possibly processed by a different system.

The flash response has a different and wider distribution over the scalp than the pattern VEP in normals, even when stimulation is confined to the same retinal areas by avoiding stimulation with stray light (Drasdo, 1982). The difference between flash and pattern VEP results in optic neuritis indicates that the two types of VEP are transmitted by completely separate fibres as early as in the optic nerve. It is even possible that the flash P2 component is transmitted to the cortex along a completely separate nongeniculate pathway (Harding and Wright, 1986). What evidence is there for nongeniculate pathways? Twenty per cent of retinal fibres are believed to travel along pathways other than the geniculostriate, such as the retinotectal pathway that passes through the superior colliculus and pulvinar to areas 18 and 19 (Wilson, 1978). In the cat, 90% of these fibres have W-type characteristics (Stone and Dreher, 1982) such as large receptive fields, sensitivity in movement and slow conducting fibres (Ikeda and Wright, 1974).

What contribution do the nongeniculate pathways make to vision? From cortical and tectal ablation experiments in hamsters, Schneider (1969) proposed that two mechanisms contribute to vision—the geniculostriate system for detailed pattern discrimination, and the superior colliculus and other tectal structures for visual location and orientation. Pasik and Pasik (1982) found that the nongeniculate systems in destriate monkeys mediate visual functions connected with luminance discrimination and space localization. The results of the work of Chalupa *et al.* (1973) on the flash VEP of the cat strengthens the possibility that the flash P2 component is transmitted along a retinotectal pathway to extrastriate cortex while the P1 component is transmitted along the geniculostriate pathway. Selective cryogenic blocking of the pulvinar and different layers of the lateral geniculate body in turn showed that the primary components of the flash VEP over the marginal gyrus (equivalent to areas 17 and 18) were transmitted by direct geniculostriate fibres while the secondary components were transmitted by fibres travelling from layer B of the lateral geniculate through the pulvinar to the suprasylvian gyrus (approximately equivalent to area 19).

Having seen from animal research that nongeniculate pathways could be involved in the transmission of the flash P2 component, what published evidence is there in man for the importance of nongeniculate pathways and also for the origins of the flash VEP? Several groups have reported that patients with complete lesions of the geniculostriate pathways still have residual 'blindsight' which is thought to be due to the functioning of nongeniculate pathways (Brindley *et al.*, 1969; Weiskrantz *et al.*, 1974; Perenin *et al.*, 1980; Barbur *et al.*, 1980; Barbur, 1984). Although the patients were not consciously aware of seeing, they demonstrated visual functions consistent with the known characteristics of the superior colliculus, such as coarse spatial summation, orientation discrimination for large targets and the ability to detect and localize flashing or fast moving stimuli.

Clearly then, nongeniculate pathways have some contribution to human vision, so how does this relate to the human VEP? Although ablation experiments cannot be carried out on humans, there are several published case histories of patients with selective lesions of the visual cortex (Corletto *et al.*, 1967; Bodis-Wollner *et al.*, 1977; Spehlmann *et al.*, 1977; Celesia *et al.*, 1980). The VEP findings in all these cases are consistent with our hypothesis that the early flash components and the pattern VEP arise in the primary visual cortex, while the later flash components are generated in the secondary or visual association areas. Several of the authors have suggested that nongeniculate pathways contribute to the VEP.

How do these theories on the origins of the VEP components relate to our temporal CSF results? Our results indicate that high temporal frequencies are transmitted along the geniculostriate pathway and are probably determined by the same mechanisms that determine pattern VEP latency. Pathology affecting low temporal frequency processing also affects the flash P2 component which, we have suggested, could be transmitted by a nongeniculate pathway. The results of the study by Schwartz and Chaney (1966) on the effect of selective lesions on the critical flicker frequency in the cat would be consistent with our theories. They concluded that the high temporal frequency system is located in the geniculostriate pathway and various posterolateral thalmic nuclei, and the low temporal frequency system is located in a parallel visual pathway through the superior colliculus and its connections.

Looking at results on humans we find that different aspects of high temporal frequency processing were reduced in 2 of the patients with lesions of the geniculostriate pathway previously discussed. One had a very poor critical flicker frequency (Barbur *et al.*, 1980) and the other had reduced critical frequency of photic driving of the VEP (Celesia *et al.*, 1980) both of which would be consistent with our hypothesis. The steady state VEP was used by Spekreijse *et al.* (1977) to investigate the functioning of the human visual system at different temporal frequencies in normals. They also concluded that the high temporal frequency response originates in the primary visual cortex and the medium frequency response in the secondary visual cortex. The authors suggested that they are mediated by parallel channels that could separate as early as the retinal ganglion cell level. The low frequency response was found to be more widely distributed over the scalp, suggesting an origin in the centres where the EEG alpha rhythm is produced. A study by our group (Bajalan *et al.*, 1986) suggested that the flash P2 component, unlike the pattern reversal VEP, is influenced by the cholinergic reticular activating system where the alpha rhythm is believed to be generated. These two observations provide further evidence for a link between the flash P2 component and low temporal frequency processing in the visual system.

The study of optic neuritis and dementia and their selective effects on the VEP and visual psychophysics has provided a unique opportunity to further our knowledge of the relationship between these measures and the information they provide about different aspects of processing in the visual system.

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THE HYPERTROPHIC FORMS OF HEREDITARY MOTOR AND SENSORY NEUROPATHY

A STUDY OF HYPERTROPHIC CHARCOT-MARIE-TOOTH DISEASE (HMSN TYPE I) AND DEJERINE-SOTTAS DISEASE (HMSN TYPE III) IN CHILDHOOD

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SUMMARY

The clinical and histopathological features in sural nerve biopsies from 10 cases of dominantly inherited hypertrophic Charcot-Marie-Tooth disease (hereditary motor and sensory neuropathy (HMSN), type I) presenting in childhood are contrasted with those of 6 cases of Dejerine-Sottas disease (HMSN type III). There was a significantly greater incidence of ataxia, areflexia and clinical nerve enlargement in HMSN type III. In HMSN type III, there was also (1) a significantly lower density of myelinated fibres 8 μm or more in diameter, (2) a greater frequency of onion bulbs, (3) more lamellae per onion bulb and, (4) a higher ratio of mean axon diameter to fibre diameter. The functional severity of the HMSN type III cases was not markedly worse than those with HMSN type I. Using these parameters, it was possible to attempt classification of sporadic cases of hereditary motor and sensory neuropathy. Cerebrospinal fluid protein levels were unreliable in distinguishing the two types of neuropathy.

INTRODUCTION

Since the original description of a hereditary 'progressive hypertrophic interstitial neuritis of childhood' by Dejerine and Sottas in 1893, there has been confusion about the clinical features, prognosis, histological characteristics and inheritance of the disorder. Indeed, several authors (Brust *et al.*, 1978; Hagberg and Westerberg, 1983) have doubted the existence of the condition as a distinct entity.

The confusion has arisen for a number of reasons. (1) Early authors were unaware that nerve hypertrophy is a nonspecific finding that can be seen in Charcot-Marie-Tooth disease, Refsum's syndrome and certain acquired neuropathies, as well as in Dejerine-Sottas disease. (2) Until the past fifteen years, few reports described the

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neurophysiological and ultrastructural features of the disease so that it is difficult to classify retrospectively many of the early reported cases. (3) Careful clinical and neurophysiological studies of relatives of the patients are lacking in most reports, making genetic analysis difficult because of the well-known phenotypic variation of hereditary peripheral neuropathies. (4) No specific biochemical abnormality has yet been detected in any of the hereditary hypertrophic neuropathies other than Refsum's disease. (5) Most authors have described small numbers of cases, without placing them in the context of other chronic peripheral neuropathies occurring in childhood.

In 1975 Dyck reclassified the hereditary motor and sensory neuropathies and proposed clinical and histological criteria for distinguishing the (usually) dominantly inherited hypertrophic form of Charcot-Marie-Tooth disease (HMSN type I) from a hypertrophic neuropathy of generally greater severity, corresponding to Dejerine-Sottas disease (HMSN type III) which appeared to be sporadic or recessively inherited. The description of HMSN type III was based on 7 patients from 5 families; 2 of the 7 patients, siblings of more typical cases, were only mildly affected.

In their study of 228 patients with hereditary motor and sensory neuropathy types I and II, Harding and Thomas (1980) found 8 cases of HMSN type I in 4 families where the inheritance appeared to be autosomal recessive. It was proposed on the basis of segregation analysis that most of the 26 sporadic cases were also recessive. Criteria for separating sporadic dominant HMSN type I cases from sporadic recessive cases were not formulated.

Westerberg (1982) has suggested that 'the designation of a special infantile hypertrophic HMSN III should be abandoned as being an artificial, and misleading concept'. The basis for the viewpoint appears to be the proposition that cases of so-called HMSN type III represent the more severely affected end of the spectrum of severity of HMSN type I and that any proposed clinical or histopathological criteria which can be advanced as distinguishing features are merely the result of selection of more severe cases for analysis. It is difficult to prove that this proposition is incorrect. However, it seems highly unlikely for the following reasons. (1) Except in the situation where *both* parents are carriers of the HMSN type I gene (Killian and Kloepfer, 1979), there is no documented instance in the literature where a child meeting the clinical criteria for the diagnosis of HMSN type III, as defined by Dyck (1975), has been born to a parent with HMSN type I. (2) In the experience of this laboratory, where over 24 kindreds containing multiple cases of HMSN type I have been studied both clinically and by sural nerve biopsy, no such situation has been observed. (3) Even in the most severely affected childhood HMSN type I cases, the pathological findings have been found in the present study to be similar to those of more typical cases of HMSN type I. They lack the characteristics of HMSN type III as defined by Dyck (1975). Thus it appears valid to propose that three forms of hypertrophic hereditary motor and sensory neuropathy exist: (1) dominantly inherited HMSN type I; (2) recessively inherited HMSN type I; and (3) HMSN type III, a recessive or sporadic condition. Whether (2) and (3) are genetically distinct cannot, at present, be stated.

In the present study, the proposition that HMSN type I and HMSN type III are distinct entities has been examined by analysing the characteristics of 16 patients with the two conditions and an attempt has been made to define more accurately those clinical, electrophysiological and pathological features that most clearly distinguish the two conditions. Other sporadic cases of hypertrophic HMSN studied in this laboratory have then been examined in the light of these findings. By so doing, it was hoped to develop criteria (1) to validate an early diagnosis, (2) to indicate the likely pattern of inheritance and (3) to compare the natural history of the disorders.

PATIENTS

Of 125 children aged 16 years and under with biopsy-proven chronic polyneuropathy studied in the authors' laboratory since 1967, 32 were found to have a hypertrophic form of hereditary motor and sensory neuropathy. The criteria for diagnosis were (1) clinical evidence of chronic polyneuropathy, (2) median nerve motor conduction velocity of 40 $m \cdot s^{-1}$ or lower, (3) histopathological evidence of onion bulb formation in biopsied sural nerve, (4) no clinical or histopathological evidence of other disease known to be associated with hypertrophic demyelinating neuropathy such as Refsum's disease or chronic inflammatory polyneuritis.

HMSN Type I

Twelve cases were known to have a parent with documented hypertrophic neuropathy. Ten of these were personally examined by one of the authors (R.A.O.) and their biopsies studied by quantitative morphometric analysis. These 10 cases are discussed in detail. Sural nerve biopsy had been performed on the parents of 2 patients and an aunt of a third, the findings being typical of HMSN type I. None of the patients in this group had spasticity, optic atrophy or other evidence of CNS disease.

HMSN Type III

There were 6 cases classified as HMSN type III. They were identified on the following basis: (1) onset within the first two years of life; (2) motor conduction velocity 12 $m \cdot s^{-1}$ or less in all peripheral nerves tested; (3) CSF protein concentration greater than 0.7 g/l; (4) no evidence of dominant inheritance—all parents were normal by history and 11 of the 12 had normal clinical and neurophysiological investigations. Histopathological criteria were not used for selection in order to allow analysis of distinctive characteristics of the two conditions.

Sporadic Cases

There were 14 cases who did not meet the criteria for inclusion in either of the above groups. These were consequently sporadic examples of hypertrophic neuropathy of unspecified type.

METHODS

Electrophysiological Techniques

Motor conduction velocities were determined in the median, ulnar and common peroneal nerves in most cases. Supramaximal stimuli were applied to each nerve at two sites and muscle action potentials were recorded, usually through surface electrodes, from the abductor pollicis brevis, abductor digiti minimi and extensor digitorum brevis muscles respectively (Walsh and McLeod, 1970). Sensory action potentials were recorded orthodromically through surface electrodes from median and ulnar nerves at the wrist on stimulating the index and little finger respectively (Dawson, 1956). Sural nerve action potentials were recorded either orthodromically in the calf or antidromically behind the lateral malleolus, in each case using surface electrodes. The stimulus was a square wave, of 0.2 ms duration. Action potentials were amplified and displayed on standard equipment. The skin temperature of upper and lower limbs measured with a thermistor ranged from 32° to 35° C.

Histological Techniques

The techniques were those routinely performed in this laboratory (Walsh and McLeod, 1970; Low *et al.*, 1978).

Whole sural nerve biopsy was performed under general anaesthesia; 3 to 4 cm of nerve were taken. One piece was fixed in Flemming's solution (acidified chromium trioxide/osmic acid) for 24 h, dehydrated in graded ethanol, embedded in paraffin wax and cut transversely in serial 7 μm sections. The sections were stained for examination by light microscopy with Kultschitzky's haematoxylin and counterstained with Van Gieson stain.

A second piece of nerve was fixed in 2.5% buffered glutaraldehyde at 4° C for 2 h, followed by Dalton's chrome osmium for 90 min. The tissue was dehydrated in graded concentrations of ethanol, passed through acetone and embedded in Spurr's resin. Toluidine blue-stained 0.5–1.0 μm sections were then prepared for light microscopy. Further sections were cut with glass or diamond knives and double stained with uranyl acetate and lead citrate before examination in a Philips 200 or 201 electron microscope.

Quantitative Studies

Morphometric studies of transverse fascicular area, myelinated fibre diameter and density were performed on sections fixed in Flemming's solution.

Fascicular Area

All fascicles were photographed and printed at an enlargement of ×250. The accuracy of the enlargement was checked by photographing a Leitz calibration slide with divisions ruled at 10 μm intervals and subjecting the negative to the same developing, enlarging and printing process. The total endoneurial areas of all fascicles were measured using the digitizer attachment (HP 9864A) of a Hewlett-Packard (9518A) programmable calculator. The results were expressed as the total transverse fascicular area of each nerve.

Myelinated Fibre Density

Photomicrographs of portions of fascicles selected according to the methods described by Dyck *et al.* (1979) were printed at an enlargement of ×1100.

The external diameter of all myelinated fibres not undergoing active degeneration was measured with a Zeiss TGZ3 particle size analyser set on the linear mode and the total number of fibres was counted. The endoneurial area of the fascicles was measured with a digitizer attachment (HP 9864A) of a Hewlett-Packard 9815A programmable calculator. The fibre density was calculated as the number of fibres/mm^2 of intraperineurial area. Histograms of fibre diameter were drawn with a plotter (HP 9862A).

Ultrastructural Studies

The techniques have been described by Low *et al.* (1978).

Unmyelinated Fibres, Denervated Schwann Cell Subunits and Collagen Pockets

Axons of unmyelinated fibres were counted and their diameters measured as described above with a Zeiss TGZ3 particle size analyser set in the linear mode on prints at a final magnification of ×9480. The numbers of denervated Schwann cell subunits and collagen pockets were counted on the prints used for measurement of unmyelinated fibres (Thomas, 1973; Sharma and Thomas, 1975).

Onion Bulbs

On the same prints used for the quantitation of unmyelinated fibres, onion bulbs and myelin thickness (d/D or 'g') ratio were examined. A mean number of 43 myelinated fibres was measured for each nerve. In some nerves, there were few remaining myelinated axons. The minimum count was 10. An onion bulb formation (OB) was defined as an axon which was surrounded by one or more concentrically orientated supernumerary Schwann cell processes. Only myelinated fibres whose OB configurations were entirely contained within a print were measured. The frequency (%) of OB formations for the total number of myelinated fibres was determined. The number of Schwann cell processes forming the OB lamellae was counted. The OB lamellae tended to inderdigitate and the number was not always uniform around the perimeter of the axon. For each OB the largest number of lamellae was counted, provided it did not exceed the minimum count by more than 1 lamella. If the difference was 2 or more the number of lamellae was scored as 1 greater than the minimum count.

Axon Diameter: Fibre Diameter (d/D or 'g' ratio)

On the same prints that were used for the analysis of onion bulbs, the axon (d) and fibre (D) diameters were measured with a millimetre rule. For fibres that were not perfectly circular, maximum and minimum diameters were measured and the mean calculated. For each nerve, the mean d/D ratio of all fibres measured was then calculated.

RESULTS

The clinical features, results of nerve conduction studies and CSF protein levels for the HMSN type I and III patients are summarized in Tables 1-4.

Hypertrophic Charcot-Marie-Tooth Disease (HMSN Type I)

The 10 fully evaluated cases of HMSN type I were aged between 9 months and 16 yrs at the time of the biopsy (mean 8.6; SD 5.5 yrs) (Table 1). They were re-examined for the purpose of this review between the ages of 2 and 23 yrs (mean 11.6; SD 6.7 yrs). There were 4 boys and 6 girls. The mother was the affected parent in 6 cases, the father in 4. Both parents were examined clinically and electrophysiologically except for Case 4, whose father was dead and for Case 9 where the mother was unavailable. The father of Case 3 was normal clinically but did not have nerve conduction studies performed.

Two patients appeared floppy in the first 12 months. The rest were considered normal until delay in achieving motor milestones, frequent falling, poor running, progressive weakness, wasting or deformity of the feet led to medical consultation. Six of the cases sought medical advice before the age of 5 yrs. Of the 10 cases, 1 (Case 4), has never walked. In 1 (Case 9), the age of walking was unknown. The other 8 cases walked between 10 months and 2 yrs (mean 1.2; SD 0.4 yrs).

Intellectual function was normal except in Case 4 where both the mother and patient appeared of borderline intelligence. The cranial nerves were intact in 5 cases. There was slight bilateral facial weakness in 3 patients. Two patients had slight terminal nystagmus. Pupillary abnormalities were absent. All but 2 cases had muscle wasting, 5 in a distal distribution and 3 in both proximal and distal groups. Some distal weakness was present in all cases, but only 3 had definite weakness of the proximal muscle groups.

TABLE 1. HMSN TYPE I: CLINICAL FEATURES

Case, sex	*Age at biopsy*	*Age at last clinical examination*	*Onset of symptoms under 1 yr*	*Age of walking*	*Pupils*	*Other cranial nerve deficits*	*Proximal weakness*	*Tendon reflexes*	*Ataxia*	*Moderate or severe sensory deficit*	*Clinically enlarged nerves*	*Deformity*
1, F	9 mo.	7 yrs	+	2 yrs	N	—	—	Absent in lower limbs TJ, SJ +	Slight	—	+	Slight scoliosis, pes cavus
2, F	19 mo.	2½ yrs	—	19 mo	N	—	—	Absent in lower limbs	—	—	—	—
3, M	3 yrs	3 yrs	—	14 mo.	N	—	—	Normal	—	—	—	—
4, F	7 yrs	7 yrs	+	Unable	N	Slight bilat. facial weakness	+	All absent	—	—	—	Flexion contracture knees, hips
5, F	8 yrs	9 yrs	—	12 mo.	N	—	—	All absent except SJ	—	—	—	Pes cavus
6, F	10 yrs	15 yrs	—	10 mo	N	—	+	SJ, AJ, absent	—	—	—	Lordosis, pes cavus
7, F	13 yrs	15 yrs	—	12 mo.	N	Slight facial weakness	+	Absent except SJ	—	+	—	Scoliosis, pes cavus
8, M	13 yrs	14 yrs	—	14 mo	N	Nystagmus	—	Absent in lower limbs	Slight	—	—	Pes cavus
9, M	14 yrs	20 yrs	—	Unknown	N	Nystagmus. Slight bilat facial weakness	—	Absent except TJ, KJ	Slight	—	+	Pes cavus
10, M	16 yrs	23 yrs	—	12 mo.	N	—	—	Absent except R TJ	—	+	—	Pes planus

+ = present; — = absent; N = normal

TABLE 2. HMSN TYPE III: CLINICAL FEATURES

Case, sex	*Age at biopsy*	*Age at last clinical examination*	*Onset of symptoms under 1 yr*	*Age of walking*	*Pupils*	*Other cranial nerve deficits*	*Proximal weakness*	*Tendon reflexes*	*Ataxia*	*Moderate or severe sensory deficit*	*Clinically enlarged nerves*	*Deformity*
11, F	2 yrs	2 yrs	+	2⅓ yrs	N	—	+	All absent	+	NE	+	—
12, M	2 yrs	10 yrs	+	2½ yrs	N	Slight bilateral facial weakness	+	All absent	+	—	+	R. hip dislocation, scoliosis, L. elbow dislocation, pes cavus
13, F	4 yrs	4 yrs	+	2 yrs	Unequal	Levre de tapir, ptosis, slight bilat. facial weakness	+	All absent	+	—	+	—
14, F	5 yrs	13 yrs	—	1 yr 2 mo.	N	Nystagmus, slight bilat. facial weakness	+	All absent	+	+	+	Pes cavus
15, M	7 yrs	9 yrs	—	1 yr 5 mo.	N	L. ptosis	—	Absent except BJ, TJ	+	+	+	Pes cavus
16, F	13 yrs	23 yrs	+	4 yrs	N	Levre de tapir, slight bilat. facial weakness	+	All absent	+	+	+	Pes cavus, scoliosis

+ = present; — = absent; N = normal; NE = not examined.

In 1 patient all tendon reflexes were absent. In 2, all reflexes except the brachioradialis jerks were absent, and in 2 patients only the triceps jerks could be elicited. The other cases had preserved upper limb reflexes; 2 of these had preserved knee jerks. One 3-year-old boy had preservation of all tendon reflexes. Three cases showed slight ataxia. Sensory changes were slight in 6 and moderately severe in 2 of the 8 type I cases in whom it could be tested.

A postural tremor was present in 4 cases. Pes cavus was seen in 6 patients. Clawing of the fingers was noted in 1 and kyphoscoliosis or excessive lordosis in 3 cases. Peripheral nerve trunks or the greater auricular or cervical nerves were definitely enlarged in 2 cases.

Dejerine-Sottas Disease (HMSN Type III)

The 6 cases of HMSN type III were aged between 2 and 13 yrs (mean 5.5; SD 3.3) at the time of the biopsy (Table 2). They were re-examined for the purpose of this review between the ages of 2 and 23 yrs (mean 10.0; SD 7.5). There were 2 boys and 4 girls. Both parents were normal to clinical and electrophysiological testing in 5 families. The father of Case 16 was unavailable for examination but was normal by history. Her mother was normal.

Four cases caused concern in the first year because of hypotonia or delayed milestones. Medical advice was sought for all HMSN type III patients before the age of 5 yrs. Later presenting complaints included delayed walking, ataxia, progressive weakness or wasting in the lower limbs. The mean age of walking was 2.3 (SD 1.0) yrs with a range of 14–48 months.

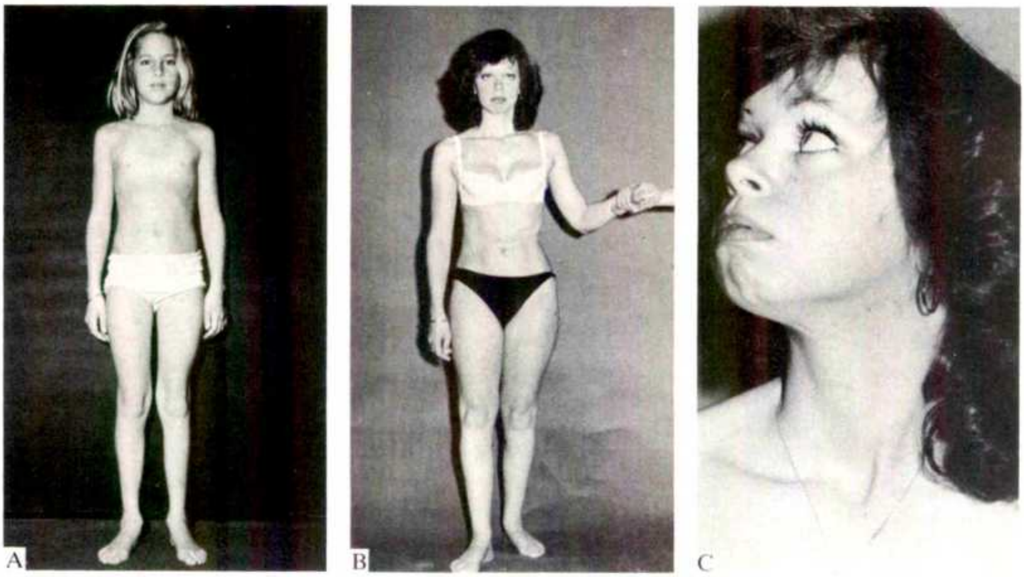

FIG. 1. A, *Case 6* (HMSN type I) at the age of 10 yrs. There is mild distal wasting of the lower limbs more marked on the left. B, *Case 16* (HMSN type III) at the age of 23 yrs. Although wasting is not evident, the patient requires support because of ataxia. C, *Case 16* (HMSN type III) at the age of 23 yrs. The thick pouting lips are prominent.

Intellectual function was normal in all cases. Four patients had slight facial weakness or had a characteristic facial appearance of prominent thick lips ('lèvre de tapir' of Dejerine and André-Thomas (1906)) or both (fig. 1). Two patients had ptosis, 1 unilateral; 1 had fine horizontal nystagmus. Case 13 had slight pupillary inequality. All patients had a normal pupillary reaction to light.

Three cases had distal wasting while 1 had both proximal and distal wasting. There was no wasting in 2 young patients. Despite the pattern of wasting, 5 cases had evidence both of distal and some proximal weakness. All tendon reflexes were absent in 5 cases; 1 case had absent knee and ankle jerks but preserved biceps and triceps jerks.

Ataxia, demonstrated by testing of tandem gait or finger/nose/finger movement, was present in all type III cases. Frequently it was the major cause of disability and was quite out of proportion to the degree of weakness. Where detailed testing was possible, a severe associated proprioceptive sensory loss was not consistently present.

Three cases had moderate or severe sensory loss, and 3 young patients no definite abnormality. Proprioception, vibration and two-point discrimination were the modalities of sensation most affected while touch and pin prick were least often involved.

One case had a postural tremor. Pes cavus was present in 4 cases and clawing of the fingers in only 1. Kyphoscoliosis was noted in 2. Peripheral nerve trunks, the greater auricular or cervical nerves were definitely enlarged in 5 of the HMSN type III cases.

The severity of functional disability was similar in both HMSN type I and III cases. All of the HMSN type I cases were ambulant except Case 4, aged 7 yrs, who had never walked. All of the HMSN type III cases were also ambulant and most were capable of walking several miles. The oldest, aged 23 yrs, used crutches because of her ataxia rather than because of weakness. None of the older patients with HMSN type III disease felt that deterioration had occurred over several years.

In comparing the HMSN type I and III patients, statistically significant differences were found for the age of walking ($P < 0.01$, Mann-Whitney test) and for the complete absence of tendon reflexes ($P < 0.05$), ataxia ($P < 0.05$) and thickening of nerves ($P < 0.05$) (Fisher's exact test).

LABORATORY INVESTIGATIONS

Nerve Conduction Studies

Except for 1 of the HMSN type I cases in whom a small median nerve sensory action potential was recorded (Case 8), sensory action potentials were absent in all nerves tested in the remaining patients in both groups (Tables 3 and 4). Motor nerve conduction velocities ranged from 12 to 40 $m{\cdot}s^{-1}$ in the upper limbs in the HMSN type I patients except for Case 4, the most severely affected patient, in whom median nerve conduction velocity was 7 $m{\cdot}s^{-1}$. By contrast, in all HMSN type III cases motor conduction velocities were 12 $m{\cdot}s^{-1}$ or lower in the upper limbs.

TABLE 3. HMSN TYPE I: INVESTIGATIONS

Conduction studies

	Motor conduction velocity			*Sensory action potentials*						
Case	*Median* ($m \cdot s^{-1}$)	*Ulnar* ($m \cdot s^{-1}$)	*Peroneal* ($m \cdot s^{-1}$)	*Latency* (*ms*)	*Median Amplitude* (μV)	*Ulnar Amplitude* (μV)	*Sural Amplitude* (μV)	*CSF protein* (*g/l*)	*Clinical score**	*Affected parent Fastest motor conduction velocity* ($m \cdot s^{-1}$)
1	20	14	NE	—	0	0	NE	NE	3	10
2	31	NE	21	—	NE	NE	NE	0.40	1	19
3	30	33	31	—	0	0	0	0.10	0	33
4	7	—	—	—	0	NE	NE	0.50	3	20
5	18	NE	15	—	0	NE	0	0.42	0	19
6	37	35	29	—	0	0	0	0.70	0	36
7	12	NE	—	—	0	NE	0	1.12	1	12
8	40	NE	40	3.4	6	NE	0	0.33	1	40
9	21	20	—	—	0	0	NE	NE	2	17
10	30	NE	NE	—	0	NE	NE	NE	0	31

* *See* text; NE = not examined.

TABLE 4. HMSN TYPE III: INVESTIGATIONS

Conduction studies

	Motor conduction velocity			*Sensory action potentials*						
Case	*Median* ($m \cdot s^{-1}$)	*Ulnar* ($m \cdot s^{-1}$)	*Peroneal* ($m \cdot s^{-1}$)	*Latency* (*ms*)	*Median Amplitude* (μV)	*Ulnar Amplitude* (μV)	*Sural Amplitude* (μV)	*CSF protein* (*g/l*)	*Serum phytanate*	*Clinical score*
11	5	NE	NE	—	0	0	NE	1.30	N	5
12	8	9	NE	—	0	0	NE	1.80	N	5
13	7	NE	—	—	0	NE	0	2.12	N	5
14	—	—	—	—	0	NE	0	0.94	N	4
15	12	NE	—	—	0	NE	0	0.72	NE	3
16	—	—	—	—	0	0	NE	0.85	NE	5

* *See* text; NE = not examined; N = normal.

Other Investigations

The CSF protein concentration was examined in 7 of the HMSN type I cases and ranged from 0.1 to 1.12 g/l (mean 0.451; SD 0.32). It was examined in all 6 of the HMSN type III cases and ranged from 0.72 to 2.12 g/l (mean 1.29; SD 0.56). The difference is significant ($P < 0.01$, Mann-Whitney Test). Plasma phytanic acid was examined in 4 of the HMSN type III cases and was normal (< 0.05 g/l) in all.

RESULTS OF HISTOPATHOLOGICAL STUDIES

HMSN Type I

Light microscopy. Total fascicular cross-sectional areas of the sural nerve of all patients and controls are shown in fig. 2 and Table 5. The increase in total fascicular area in some nerves was accompanied by an apparent increase in endoneurial collagen and by onion-bulb formations. This increase in sural nerve cross-sectional area did not correlate well with clinical estimates of nerve enlargement at the review examination.

Minimal changes only (such as very small onion bulbs and occasional degenerating fibres), were seen under the light microscope in very young patients but by the age of 7 yrs, loss of fibres, thin myelin sheaths of some fibres and definite onion-bulb formations were evident (fig. 3). There was an increase in the frequency of onion bulbs with increasing age (fig. 4). Fibre diameter distributions are shown in fig. 5.

The morphometric data on myelinated fibres are summarized in Table 5. The myelinated fibre density of the group ranged from 1.51 to $9.35 \times 10^3/\text{mm}^2$ (mean 4.95; SD 2.79). When the values of mean myelinated fibre density in the present series are plotted against control values in the paediatric age range (Ouvrier *et al.*, 1986), it is apparent that there is a decrease in myelinated fibre density in most cases

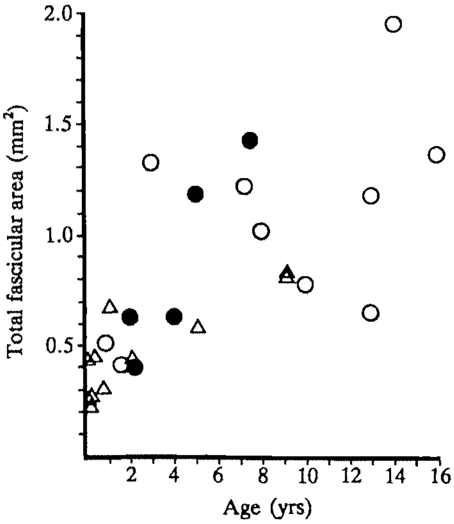

FIG. 2. Total fascicular cross-sectional area in sural nerve of controls (▵), HMSN type I patients (○) and HMSN type III patients (●).

TABLE 5. HMSN TYPE I: TRANSVERSE FASCICULAR AREA AND MYELINATED FIBRE DENSITIES

					Density of fibres ≥ 8 μm	
Case	*Age*	*Sex*	*Total transverse fascicular area (mm^2)*	*Density (10^3 fibres/mm^2)*	*(10^3 fibres/mm^2)*	*(% of total)*
1	9 mo.	F	0.509	9.35	4.51	48
2	19 mo.	F	0.409	7.15	3.38	45
3	3 yrs	M	1.324	6.85	2.42	35
4	7 yrs	F	1.223	2.39	1.05	44
5	8 yrs	F	1.023	5.80	2.74	47
6	10 yrs	F	0.777	1.51	0.11	7
7	13 yrs	F	0.659	2.20	0.87	40
8	13 yrs	M	1.188	6.77	1.00	15
9	14 yrs	M	1.963	1.56	0.97	62
10	16 yrs	M	1.372	5.94	0.86	15
			Mean	4.95	1.79	36
			SD	2.79	1.40	17.7

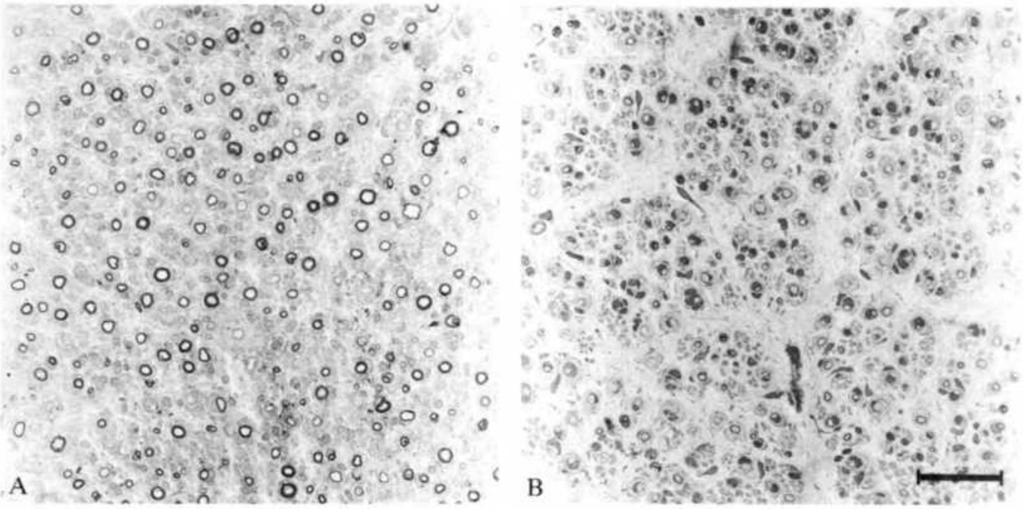

FIG. 3. A, transverse section of sural nerve of *Case 4*, aged 7 yrs (HMSN type I). Toluidine blue. B, transverse section of sural nerve of *Case 11*, aged 2 yrs (HMSN type III). Toluidine blue. Bar = 50 μm.

(fig. 6). The mean proportion of fibres equal to or greater than 8 μm in diameter was 36.0% (SD 17.7).

Electron microscopy. Electron microscopy confirmed the loss of myelinated fibres in most nerves. Onion-bulb formations were seen in all nerves but were very variable in frequency and size. Nerves of the youngest patients tended to contain less frequent and smaller onion bulbs than those of older patients (fig. 7). Most myelinated fibres were well myelinated but some thin myelin sheaths were seen. The onion-bulb lamellae in all cases contained generous amounts of cytoplasm with normal organelles. Unmyelinated fibres were frequently interpolated in the Schwann cell lamellae. Onion bulbs containing double basement membrane lamellae, although seen occasionally, were not common. Clusters of small myelinated fibres were occasionally observed, especially in Cases 6, 8 and 9. Myelin debris, consisting of clumps and ovoids, was noted in some Schwann cells and macrophages were seen in a few nerves. At times the evidence of myelin destruction was florid and much more marked than usual in older patients with HMSN type I.

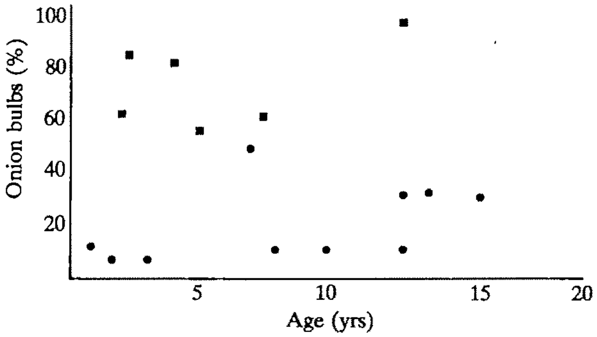

FIG. 4. Frequency of onion bulbs vs age in HMSN type I (●) and HMSN type III (■).

The mean axon diameter/fibre diameter (d/D, g) ratio ranged from 0.59 to 0.69 (mean 0.63; SD 0.04; 95% confidence limits 0.55–0.71). The density of unmyelinated fibres ranged from 1.25 to 10.92 × 10^4/mm^2 (mean 5.06; SD 2.68). The values in 3 control nerves (Ouvrier *et al.*, 1981) were 9.35, 4.99 and 3.08 × 10^4/mm^2 at the ages of 2, 9 and 13 yrs respectively. The density of denervated Schwann cell subunits ranged from 0 to 1.45 × 10^3/mm^2 (mean 0.38; SD 0.56). The density of collagen pockets ranged from 0.16 to 3.11 × 10^3/mm^2 (mean 1.71; SD 1.07). The results of quantitative studies are summarized in Table 7.

HMSN Type III

Light microscopy. The total fascicular cross-sectional areas of the sural nerve of all patients and controls are shown in fig. 2 and Table 6. In all but Case 12, there was a marked reduction in the density of myelinated fibres. Transverse sections of Cases 11, 14 and 16 were almost devoid of myelinated fibres. Particularly in the sections stained with toluidine blue, it was evident that most large axons were surrounded by conspicuous onion bulb formations. Schwann cells were prominent and myelin sheaths were frequently thin. The myelinated fibre density of the 6 patients is shown in Table 6 and histograms of myelinated fibre diameter distribution are shown in

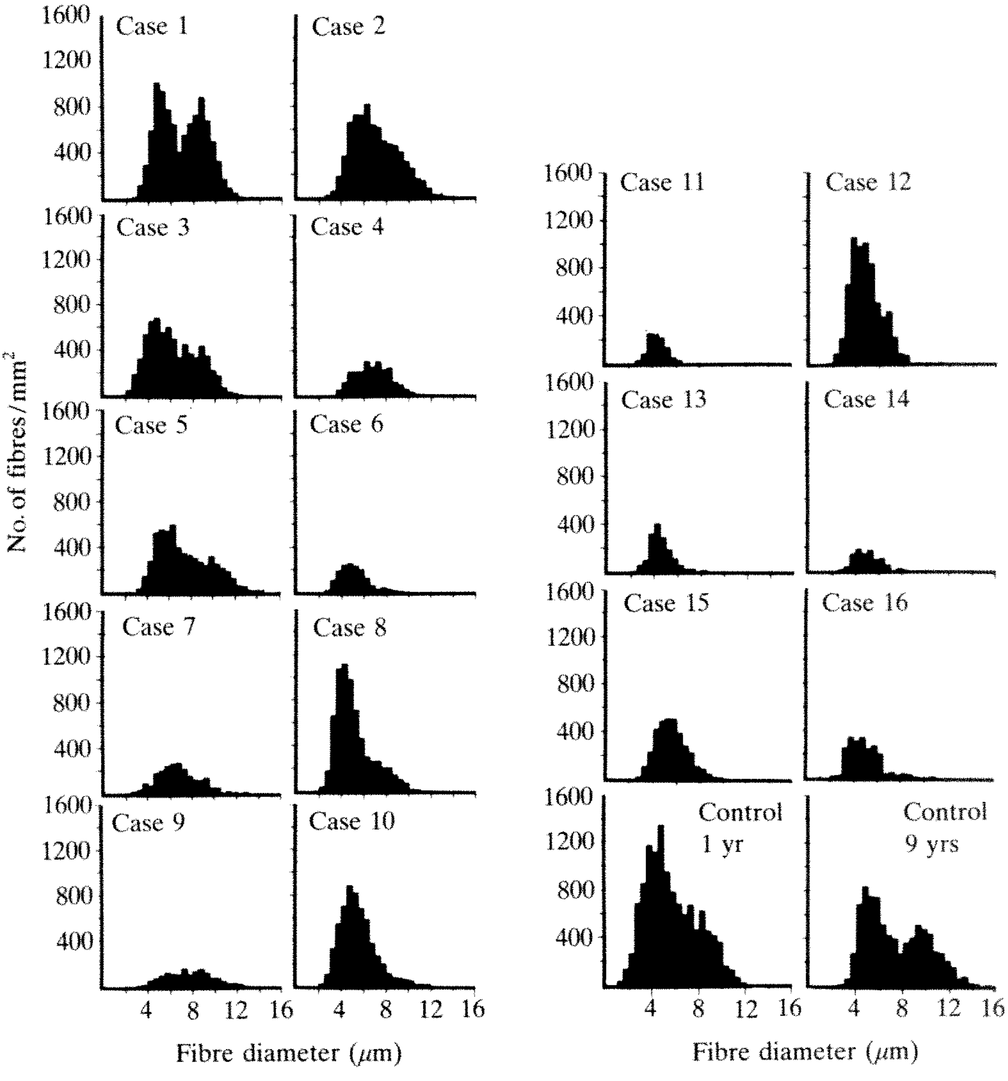

FIG. 5. Distribution of diameters of myelinated fibres in sural nerves of the 10 HMSN type I and 6 HMSN type III cases.

fig. 5. The myelinated fibre density ranged from 0.61 to 6.65 × 10^3/mm^2 (mean 2.14; SD 2.27); 4.5% (SD 5.3) of fibres were equal to or greater than 8 μm in diameter.

Electron microscopy. Even in the youngest patients, many axons were surrounded by an onion-bulb formation. The onion-bulb lamellae contained little cytoplasm and frequently consisted of apposed double basement membranes (fig. 7). Schwann cell nuclei were very prominent. Occasional macrophages were seen and myelin debris was sometimes evident in macrophages and Schwann cells.

The quantitative analysis of unmyelinated fibres and of onion bulbs is shown in

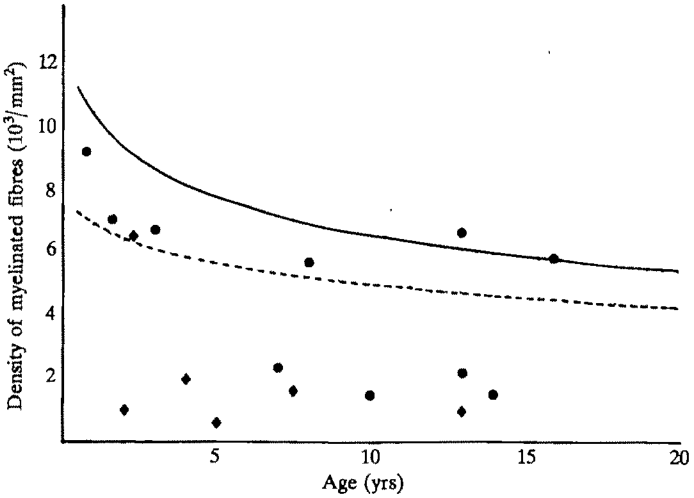

FIG. 6. Density of myelinated fibres versus age in HMSN type I (●) and HMSN type III (◆). The predicted normal mean (continuous line) and fifth centile (interrupted lines) values are also shown.

TABLE 6. HMSN TYPE III: TRANSVERSE FASCICULAR AREA AND MYELINATED FIBRE DENSITIES

Case	*Age*	*Sex*	*Total transverse fascicular area* (mm^2)	*Density* (10^3 *fibres*/mm^2)	*Density of fibres* ≥ *8 μm* (10^3 *fibres*/mm^2)	(% *of total*)
11	2 yrs	F	0.633	1.02	0	0
12	2 yrs 3 mo.	M	0.400	6.65	0.40	6
13	4 yrs	F	0.628	1.98	0.09	5
14	5 yrs	F	1.177	0.61	0.09	14
15	7½ yrs	M	1.425	1.59	0.04	2
16	13 yrs	F	(Fascicular biopsy)	0.96	0.03	0
			Mean	2.14	0.11	4.5
			SD	2.27	0.15	5.3

TABLE 7. HMSN TYPE I: ULTRASTRUCTURAL FINDINGS

Case, sex	*Age*	*Density of unmyelinated fibres* (10^4 *fibres*/mm^2)	*Onion bulbs* (%)	*Onion-bulb lamellae* (*mean no. per onion bulb*)	*g ratio*	*Collagen pockets* (10^3 *fibres*/mm^2)	*Denervated Schwann cell subunits* (10^3 *fibres*/mm^2)
1, F	9 mo.	10.92	12	1.14	0.62	3.11	0.00
2, F	19 mo.	5.41	7	1.13	0.59	0.42	0.00
3, M	3 yrs	5.96	7	1.00	0.60	1.60	0.00
4, F	7 yrs	3.17	50	1.22	0.61	1.96	0.71
5, F	8 yrs	2.37	11	1.25	0.62	0.16	0.00
6, F	10 yrs	4.47	11	1.00	0.66	2.10	1.45
7, F	13 yrs	1.25	32	2.00	0.67	0.28	0.00
8, M	13 yrs	4.75	11	1.67	0.69	2.38	0.41
9, M	14 yrs	6.90	33	1.00	0.59	2.86	1.19
10, M	16 yrs	5.43	31	1.00	0.65	2.18	0.00
	Mean	5.06	20.5	1.24	0.63	1.71	0.38
	SD	2.68	14.8	0.34	0.04	1.07	0.56

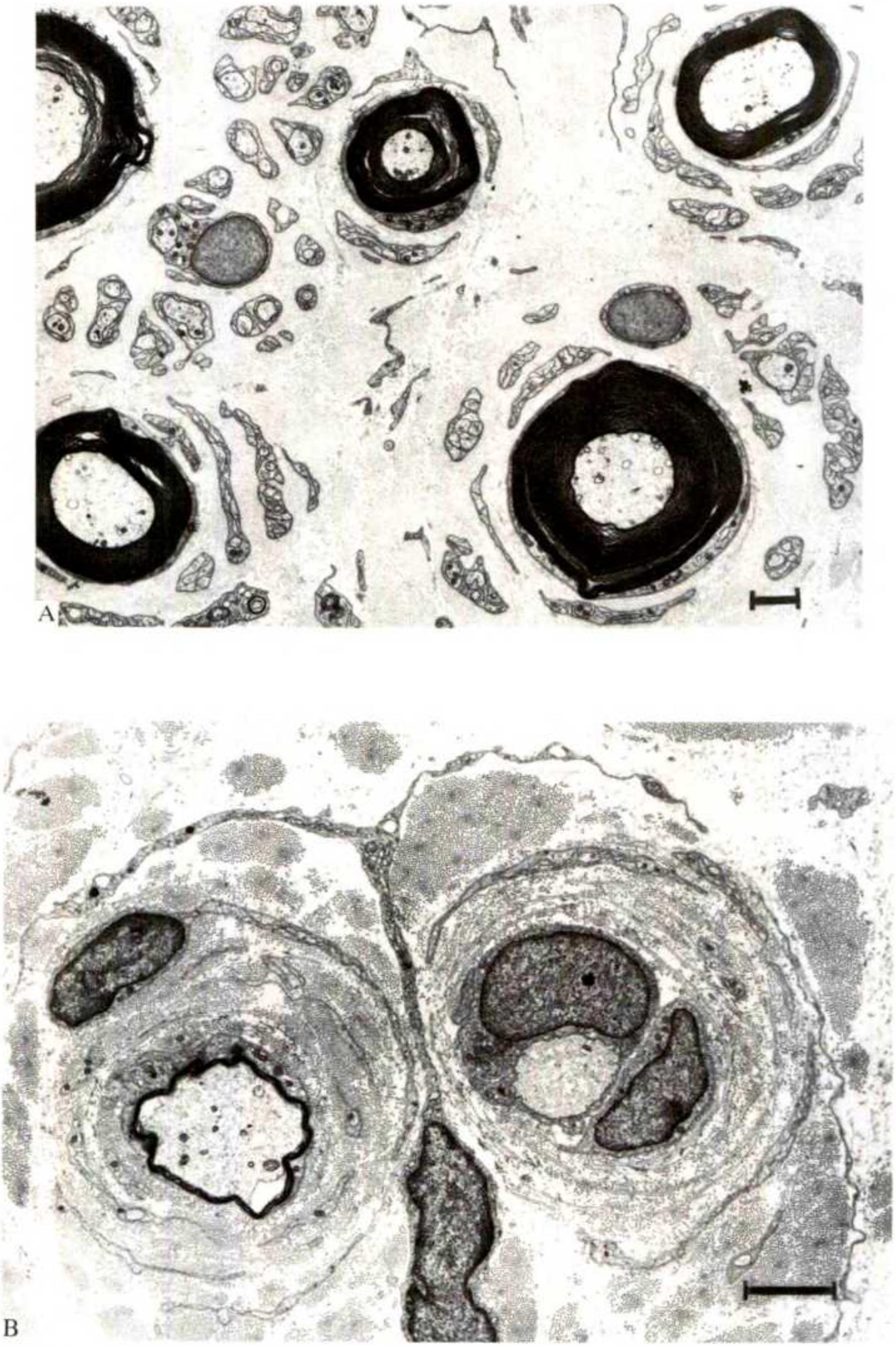

FIG. 7. Representative electron micrographs. A, HMSN type I (*Case 4*, aged 7 yrs). Several small incompletely formed onion bulbs are seen. Abnormal variability of myelin thickness is also evident. B, HMSN type III (*Case 11*, aged 2 yrs). Large onion bulbs are seen containing small fibres with absent or very thin myelin sheaths. Bars = 3 μm.

TABLE 8. HMSN TYPE III: ULTRASTRUCTURAL FINDINGS

Case, sex	*Age*	*Density of unmyelinated fibres (10^4 fibres/mm^2)*	*Onion bulbs (%)*	*Onion-bulb lamellae (mean no. per onion bulb)*	*g ratio*	*Collagen pockets (10^3 fibres/mm^2)*	*Denervated Schwann cell subunits (10^3 fibres/mm^2)*
11, F	2 yrs	4.99	63	3.42	0.82	3.4	0.00
12, M	2 yrs 3 mo.	3.25	86	1.55	0.82	4.8	0.15
13, F	4 yrs	2.77	83	2.52	0.85	1.7	0.00
14, F	5 yrs	4.27	57	1.41	0.84	1.7	0.90
15, M	7½ yrs	2.01	62	2.39	0.81	0.7	0.00
16, F	13 yrs	2.29	100	3.87	1.00	0.1	0.00
	Mean	3.26	75	2.53	0.86	2.07	0.18
	SD	1.16	17	0.98	0.07	1.75	0.36

Table 8. The mean axon diameter: fibre diameter (g) ratio was 0.86 (SD 0.07; 95% confidence limits 0.72–1.00). The density of unmyelinated fibres ranged from 2.01 to $4.99 \times 10^4/\text{mm}^2$ (mean 3.26; SD 1.16). The density of denervated Schwann cell subunits ranged from 0 to $0.90 \times 10^3/\text{mm}^2$ (mean 0.18; SD 0.36), and the density of collagen pockets from 0.10 to $4.8 \times 10^3/\text{mm}^2$ (mean 2.07; SD 1.75).

In comparing the HMSN type I and III nerves, statistically significant differences were found for the density of myelinated fibres 8 μm or more in diameter ($P = 0.003$), the frequency of onion bulbs ($P = 0.001$), the number of lamellae per onion bulb ($P = 0.006$) and the ratio of mean axon diameter to fibre diameter (g) ratio ($P = 0.001$) (Mann-Whitney Test).

COMPARISON OF HMSN TYPE I, HMSN TYPE III AND SPORADIC HYPERTROPHIC HMSN

The findings on clinical and special investigations for the sporadic cases of hypertrophic HMSN are listed in Tables 9 and 10. The axon/fibre diameter (g) ratio is also listed in Table 10. Other morphometric data were not analysed in detail.

If the four clinical characteristics which reached statistical significance in the comparison of type I and III (i.e., age of walking greater than 14 months, complete absence of tendon reflexes, ataxia and clinical enlargement of nerves) are combined with nerve conduction velocity, a clinical score can be assigned to each patient. If one point is given for the presence of each of the four parameters and one for median nerve conduction velocity of 12 m·s^{-1} or lower, then a total score of 5 points could be reached.

In the HMSN type I patients, the mean clinical score was 1.1 (SD 1.2). Only 2 HMSN type I patients scored 3 points. Among the HMSN type III patients, the mean clinical score was 4.5 (SD 0.8). Only 1 of the HMSN type III patients scored 3 points. Thus there was a slight overlap of clinical parameters, which did not allow distinction of HMSN type I and type III cases on clinical grounds alone.

TABLE 9. HYPERTROPHIC HMSN: SPORADIC CASES, CLINICAL FEATURES

Case	*Sex*	*Age at biopsy*	*Age at last clinical examination*	*Onset of symptoms under 1 yr*	*Age of walking*	*Pupils*	*Other cranial nerve deficits*	*Proximal weakness*	*Tendon reflexes*	*Ataxia*	*Moderate or severe sensory deficit*	*Clinically enlarged nerves*	*Deformity*
17	M	18 mo.	13 yrs	—	2 yrs 2 mo.	N	—	—	Absent except TJ	—	—	+	Bilat. pes cavus, scoliosis
18	F	2 yrs	2 yrs	—	13 mo.	N	—	—	Absent except TJ	±	—	—	Valgus feet
19	M	3 yrs	11 yrs	+	3 yrs	N	Nystagmus	+	All absent	+	+	+	Scoliosis
20	M	3 yrs	7 yrs	—	3 yrs	N	—	+	All absent	+	+	+	Pes cavus, scoliosis
21	M	4 yrs	15 yrs	+	4 yrs	R slightly irregular	—	+	All absent	+	+	+	Pes cavus, scoliosis
22	F	4 yrs	10 yrs	+	20 mo.	N	Prominent lips	+	All absent	+	—	+	Pes cavus
23	M	4 yrs	6 yrs	—	14 mo.	N	Nystagmus, deafness	—	Absent except TJ	+	—	+	Bilat. pes cavus
24	M	5 yrs	15 yrs	—	18 mo.		Oculomotor paresis	+	Absent except BJ	+	—	+	Bilat. pes cavus
25	F	6 yrs	6 yrs	—	3 yrs	N	—	—	Absent KJ, AJ	—	—	—	Bilat. pes cavus
26	M	12 yrs	13 yrs	—	17 mo.	N	Nystagmus	—	Absent except BJ, TJ	±	—	+	Bilat. pes cavus
27	M	12 yrs	12 yrs	—	15 mo.	N	Nystagmus	±	Absent KJ, AJ	+	±	—	Bilat. pes cavus
28	F	15 yrs	21 yrs	—	Unknown	N	—	+	Absent except TJ	—	+	+	Bilat. pes cavus
29	M	15 yrs	15 yrs	—	11 mo.	N	—	+	Absent except TJ	+	—	—	Bilat. pes cavus
30	M	15 yrs	18 yrs	—	Average	N	—	+	Absent except BJ, TJ	—	+	+	Scoliosis, bilat. pes cavus

N = normal.

TABLE 10. HYPERTROPHIC HMSN: SPORADIC CASES, INVESTIGATIONS

					Sensory action potentials								
		Motor conduction velocity			*Median*		*Ulnar*		*Sural*				
Case	*Sex*	*Median* ($m \cdot s^{-1}$)	*Ulnar* ($m \cdot s^{-1}$)	*Peroneal* ($m \cdot s^{-1}$)	*Latency* (*ms*)	*Amplitude* (μV)	*Latency* (*ms*)	*Amplitude* (μV)	*Latency* (*ms*)	*Amplitude* (μV)	*CSF protein* *g/l*	*Clinical score**	*g ratio*
17	M	13	NE	—	—	0	—	0	—	NE	NE	2	0.71
18	F	20	NE	14	—	0	—	NE	—	0	0.71	1	0.63
19	M	8	10	10	—	0	—	0	—	0	0.20	5	0.70
20	M	10	NE	8	—	0	—	NE	—	0	0.23	5	0.80
21	M	8	—	—	—	0	—	0	—	NE	NE	5	0.74
22	F	12	8	—	—	0	—	0	—	NE	0.60	5	0.75
23	M	18	NE	12	—	0	—	NE	—	0	0.38	2	0.56
24	M	—	—	—	—	0	—	NE	—	NE	1.10	4	0.71
25	F	23	NE	15	—	0	—	NE	—	0	0.26	1	0.60
26	M	30	19	NE	—	0	—	NE	—	0	0.65	3	0.76
27	M	16	19	NE	—	0	—	NE	—	0	NE	2	NE
28	F	24	13	—	—	0	—	0	—	NE	NE	1	0.62
29	M	30	NE	9	5	5	—	NE	—	0	0.81	1	0.72
30	M	17	18	9	—	0	—	0	—	NE	NE	1	0.56

* *See* text; — = no response; NE = not examined.

In the morphometric analysis, the only parameter which absolutely distinguished the HMSN type I from the HMSN type III cases was the axon diameter/fibre diameter (g ratio). In the 10 HMSN type I cases, there was no value above 0.69, whereas among the HMSN type III cases no value fell below 0.81. Applying these parameters to the sporadic cases, the 8 cases whose clinical scores were 2 or lower had g ratios of 0.72 or below. They almost certainly represent sporadic dominant HMSN type I cases. The 6 cases with scores of 3 or greater had g ratios of 0.70 or more. These cases may represent either recessive forms of HMSN type I or sporadic type III cases (*see* Discussion below). In this respect, Case 20 would have been regarded as a clinically typical case of HMSN type III except that his CSF protein level was only 0.20 g/l.

DISCUSSION

In the present series, the definition of HMSN type I and the clinical features as described in childhood conform with the descriptions of Dyck (1975), Buchthal and Behse (1977), Harding and Thomas (1980), Vanasse and Dubowitz (1981) and Westerberg (1982). However, there is probably an over-representation of more severely affected cases than in a total population of childhood cases of HMSN type I. Biopsies are not routinely performed on all cases of HMSN type I in the authors' clinic. Cases presenting early in life or having unusually severe clinical features are more likely to have been selected. That the clinical features of HMSN type I can be so severe as to prevent walking (Case 4) or to cause fairly severe disability in late childhood has been adequately documented in previous reports (Baker and Upton, 1979; Hagberg and Lyon, 1981; Vanasse and Dubowitz, 1981).

For the most part, previous descriptions of HMSN type III have been confined to small groups of patients reported in isolation. The authors are not aware of any systematic comparison of groups of children suffering from these two types of neuropathy, prior to the present study.

The criteria for diagnosis of HMSN type III are those of Dyck (1975). The clinical features of the 6 HMSN type III cases in this series may be summarized as follows. In the majority of cases hypotonia or delay in developmental milestones or both are noticed within the first year of life. Mean age of walking is often delayed beyond the second year and coordination is never fully normal. Ataxia is seen in all patients. Proximal weakness and deformity of the hands and feet are not frequent in early childhood but become increasingly more obvious with advancing age so that by the second decade, proximal weakness is the rule rather than the exception. Clinical hypertrophy of nerves is present in most HMSN type III patients; by contrast it was noted in only a quarter of those with HMSN type I. By the time adequate testing can be performed, moderate to severe sensory loss is present in the majority of patients. Such sensory loss is rarely seen in HMSN type I cases. In the present study, the overall degree of functional disability was similar in the two groups. Facial weakness or the unusual thick-lipped pouting appearance of the face reported first by Dejerine

(1896) ('lèvre de tapir') was an interesting feature noted in the present series of HMSN type III patients (fig. 1). As in the series of Dyck (1975), no significant pupillary abnormalities were seen. Indeed, the only acceptable cases of HMSN type III of childhood onset reported in the literature to have sluggishly reacting pupils are the original cases of Dejerine and colleagues, at least 1 of whom had had syphilis (Dejerine and André-Thomas, 1906) and 2 of the cases described by Wolf *et al.* (1932). It is clear from early reports (Dejerine and André-Thomas, 1906) that the pupillary abnormalities take years to develop, thus possibly explaining the rare appearance of such changes in childhood.

Despite the probable bias towards more severely affected cases of HMSN type I disease in the present series, a distinction between HMSN type I and HMSN type III could be made on clinical, electrophysiological or histological grounds. If the two groups are compared using the statistically significant clinical distinguishing features—delay in walking, total tendon areflexia, ataxia and enlarged nerves, combined with the nerve conduction velocity (median MNCV 12 $\mathrm{m{\cdot}s^{-1}}$), it is noted that only 2 of the HMSN type I group had three of these findings, the rest having two or less. In the HMSN type III group, 5 had at least four of these features; 1 had only three of the features. Despite the difference in frequency of clinical features, the functional disability was similar in the two groups.

In contrast to the 6 cases of HMSN type III reported in the present series, which are similar to those reported by Dejerine and Sottas (1893), O'Brien (1968) and Dyck (1975) and which represent an unselected group of HMSN type III patients, there are several reports of a severe neuropathy with onion-bulb formation, commencing in the first year of life, often with severe clinical manifestations (including early death at times) and associated with hypomyelination (Lyon, 1969; Anderson *et al.*, 1973; Joosten *et al.*, 1974; Kennedy *et al.* 1977; Koto *et al.*, 1978; Moss *et al.*, 1979; Guzzetta *et al.*, 1982). In all of these case reports, there was a marked deficit in myelin sheaths, but many of the poorly myelinated axons were surrounded by onion-bulb formations, often of the double basement membrane configuration considered by Dyck (1975) to be characteristic of HMSN type III. Although some of these patients had not been able to walk by the time of reporting at 3 or 5 years of age, several had managed to do so. Guzzetta and colleagues (1982) have recently argued that these cases represent merely a subtype of HMSN type III. The cases of Karch and Urich (1975), Kasman *et al.* (1976), Palix and Coignet (1978) and Hakamada *et al.* (1983), represent a congenital neuropathy in which there is markedly diminished myelin production in the peripheral nervous system unaccompanied by the formation of onion bulbs. These cases therefore cannot strictly be classified as hypertrophic neuropathies and may therefore not belong to the general rubric of HMSN type III (Guzzetta *et al.*, 1982).

Histopathological Aspects

The characteristics of HMSN type I in this series of childhood cases did not differ qualitatively from those previously described in adults by Dyck (1975), and by Low *et al.* (1978) in this laboratory. The mean myelinated fibre density of 5.19×10^3 fibres/mm^2 compares with a mean myelinated fibre density of 1.38×10^3/mm^2 in the 15 patients aged 15 to 60 yrs of Low *et al.* (1978) and a mean control adult value of 4.57×10^3/mm^2. Although the mean density is higher than that of adults, there is an actual decrease in myelinated fibre density when comparison is made with controls of corresponding age (fig. 6). The relative loss of large diameter fibres, coupled with the relatively slight increase in transverse fascicular area (fig. 2), indicate that there is an actual loss of large diameter fibres rather than a fall in density due entirely to the increase in endoneurial area. Such a loss was shown by Dyck *et al.* (1970) and by vanWeerden *et al.* (1982).

The 3 youngest patients in the series had minimal changes on light microscopic examination and these were paralleled by the mildness of clinical manifestations and less marked slowing of nerve conduction velocity. Gutmann *et al.* (1983) have shown that abnormalities of nerve conduction evolve over the first 3 to 5 years of life in patients with dominant HMSN type I. The authors' experience is identical. Thus some patients with dominant HMSN type I have motor conduction velocities in the normal range during the first year of life. Such findings are consistent with the minimal histopathological changes seen in the very young patients. Meier *et al.* (1976) have shown an increase in onion-bulb formations in serial biopsies of children with HMSN type I. Their finding of a complete loss of large diameter myelinated fibres in early biopsies was not confirmed in the present study. Fig. 4 illustrates the progressive increase in onion bulb frequency when related to age.

The present study confirms the normal density of unmyelinated fibres in HMSN type I (Dyck *et al.*, 1970; Ouvrier *et al.*, 1981), although there is evidence of an increase in the numbers of small diameter unmyelinated fibres, possibly representing regenerating myelinated and unmyelinated fibres (Low *et al.*, 1978). Four patients showed an apparent increase in the number of empty Schwann cell subunits when compared with the nerves of 3 control children (Ouvrier *et al.*, 1981). Similarly, there was a trend towards an increase in the density of collagen pockets when compared with age-related controls. These findings indicate unmyelinated fibre degeneration (Aguayo *et al.*, 1973; Thomas, 1973; Behse *et al.*, 1975). The mean ratio of axon diameter/fibre diameter (d/D or 'g') ratio, which is a measure of the thickness of the myelin sheath, of 0.63 (± 0.04) did not differ significantly from that of 0.60 found by Low *et al.* (1978) in adults with HMSN type I.

In the HMSN type III cases, there was a marked reduction in myelinated fibre density with very few fibres over 8 μm in diameter. Electron microscopy confirmed normal numbers of unmyelinated fibres. There appeared to be some increase in collagen pockets in some nerves with no definite increase in empty Schwann cell subunits. These observations are in agreement with the limited quantitative data on the morphometry of sural nerve biopsies in HMSN type III reported in the literature (Weller, 1967; Dyck and Gomez, 1968; Lyon, 1969; Dyck *et al.*, 1970; Joosten *et al.*, 1974; Dyck, 1975; Guzzetta *et al.*, 1982).

When the morphometric data for the patients with HMSN type I were compared with those in the HMSN type III group, statistically significant differences were found for: (1) the density of myelinated fibres 8 μm or more in diameter; (2) the frequency of onion bulbs; (3) the number of onion-bulb lamellae; and (4) the ratio of mean axon diameter/fibre diameter (g ratio). Of these parameters, only the g ratio showed no overlap between the two groups. Combining the data of Low *et al.* (1978) and the present series, of 25 patients with dominant HMSN type I whose ages ranged from 9 months to 57 years, none has shown a g ratio higher than 0.69.

The recent evidence that HMSN type I kindreds can be divided into two subtypes, one linked with the Duffy blood group and one not so associated, points to the probability of genetic heterogeneity even in HMSN type I. Linkage studies have recently been commenced in some of the families in the present series, but no data are yet available which would indicate a difference in the clinical or pathological characteristics of the two subtypes (Guiloff *et al.*, 1982; Bird *et al.*, 1983; Dyck *et al.*, 1983).

The pathogenesis of both HMSN I and HMSN III remains uncertain. Since both conditions are probably heterogeneous, it seems unlikely that any single mechanism exists in either case. Although earlier studies had suggested that in HMSN I there was a primary abnormality of the synthesis or maintenance of myelin (Dyck, 1966; Dyck and Lambert, 1968), more recent evidence suggests that segmental demyelination is secondary to a primary axonal atrophy (Dyck, 1984). In view of the presence of numerous demyelinated fibres with high g ratios, the relatively normal mean g ratio implies the presence of some fibres in which the myelin sheath is relatively thick due to axonal atrophy. Such excessively thick myelin sheaths were described by Behse and Buchthal (1977), a finding which supports Dyck's hypothesis. Results of studies with nerve xenografts have been conflicting: Aguayo *et al.* (1978) reported impaired myelination of axons regenerating through transplanted HMSN I grafts, but Dyck *et al.* (1978) found no abnormality of myelination.

In HMSN III the very defective myelination of axons suggests that there is a defect in Schwann cell function, although an additional abnormality of the axon cannot be excluded. Impaired axonal transport in HMSN III lends some support to the concept of a primary neuronal abnormality (Brimijoin *et al.*, 1973). Nerve xenograft studies have not been conclusive (Dyck *et al.*, 1978). The understanding of the pathogenesis of the conditions must await the revelation of their primary genetic and biochemical defects.

Sporadic Cases of Hypertrophic HMSN

It appears from the analysis of the HMSN type I and III cases, as defined in the Introduction, that there is a clear distinction between the two groups but that some overlap of clinical criteria occurs in individual cases. Such a finding is in keeping with the mild involvement of several siblings of typical HMSN type III cases reported by Dyck (1975). Overlap was also seen in the motor nerve conduction velocities of the two types.

In the present study, the only parameter for differentiation which showed no overlap was the g ratio, values below 0.70 being seen only in type I cases and values above 0.80 being seen only in type III cases. The 95% confidence limits for g ratios of HMSN types I and III were 0.55–0.71 and 0.72–1.00, respectively.

In the Dyck (1975) classification of hereditary motor and sensory neuropathies, no category was included for a recessive form of HMSN type I. Harding and Thomas (1980) considered 8 of 138 HMSN type I cases to be of recessive inheritance and estimated from segregation analysis that 70% of single generation type I cases were of autosomal recessive inheritance. They distinguished these cases from HMSN type III on the basis of clinical and histopathological findings without giving the precise basis for the distinction.

It seems reasonable to suggest that those sporadic patients in the present study who attained clinical scores of less than three and whose g ratio was less than 0.70 are likely to be carriers of the dominant gene. Those with scores of four or more and a g ratio of more than 0.80 are likely to be (recessive) examples of HMSN type III. The classification of those patients with intermediate clinical scores of three or four and g ratios of 0.70–0.80 remains uncertain. They are probably mainly examples of 'recessively-inherited HMSN type I' or mildly affected cases of HMSN type III. However, it is not yet clear whether 'recessively inherited HMSN type I' is genetically distinct from HMSN type III. Proof of the above hypothesis will have to await the finding of a specific marker for each condition or until studies of the next generation can be undertaken.

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STUDIES ON THE AETIOLOGY AND PATHOGENESIS OF MOTOR NEURON DISEASES

1. LATHYRISM: CLINICAL FINDINGS IN ESTABLISHED CASES

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SUMMARY

Lathyrism is a toxic disease of the motor system constantly associated with primary consumption of the seed of *Lathyrus sativus* (chickling or grass pea). Neurological examination was performed on 38 affected subjects drawn from four regions of the Indian subcontinent endemic for lathyrism. All showed a consistent and largely symmetric pattern of neurological deficit similar to that displayed by 5 Europeans with longstanding lathyrism now living in Israel. Hallmarks of lathyrism include a pyramidal pattern of motor weakness combined with greatly increased tone in the thigh extensors and adductors and in the gastrocnemius muscles so that the more severely affected walk on the balls of their feet with a lurching scissoring gait. Extensor plantar responses are uniformly present in such cases, and the knee and ankle tendon reflexes are exaggerated and often clonic. Hoffmann signs and exaggerated biceps and/or triceps tendon jerks are also found in the most severely affected. Sensory signs are absent, although perverse sensations in the legs are frequently reported at the onset. Walking difficulties commonly begin suddenly but may also appear subacutely or insidiously. Some individuals experience partly reversible symptoms suggestive of a diffuse CNS excitation of somatic, motor and autonomic function.

INTRODUCTION

Lathyrism, an ancient neurodegenerative disorder now unknown in the West, is a form of spastic paraparesis that affects individuals who rely on the chickling pea (*Lathyrus sativus*) as a staple or as an emergency food during flood or following drought (Ganapathy and Dwivedi, 1961; Gardner and Sakiewicz, 1963; Spencer *et al.*, 1984). An accompaniment of war, pestilence and famine, historically lathyrism

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has affected certain human and animal populations that reside between 10 and 55° latitude and 15° W and 105° E longitude, a broad belt which, in addition to other parts of Southern Eurasia and North Africa, includes Bangladesh, NW China, Ethiopia, Greece, Israel, India, Spain and W. Germany, the current loci of known cases (Mertens, 1947; Paissios and Demopoulos, 1962; Moya *et al.*, 1967; Gebre-ab *et al.*, 1978; Cohn and Streifler, 1981; Mannan, 1985; L. Xiuyun, 1985, personal communication). Lathyrism remains common in endemic zones of Bangladesh, Ethiopia and India, with prevalence figures ranging between 0.3% and 2.5% in the regions of India and Bangladesh included in this study (Kaul and Islam, 1982; Gopalan *et al.*, 1983; Anonymous, undated). In the Rajshahi and Kushtia districts of NW Bangladesh, an area approximately four times the size of Greater London, this prevalence translates into approximately one case per square kilometre. Subjects with lathyrism drawn from this region and from Central India are compared in the present study with Europeans who developed the disorder during the Second World War (Kessler, 1947; Cohn and Streifler, 1981).

Lathyrism is more common amongst males than females, and the latter are usually among the less severely impaired in an affected community (Ganapathy and Dwivedi, 1961). The most heavily involved age ranges are between 5 and 40 years in males and between 6 and 20 years in females, although cases have been reported between 2 and 70 years (Paissios and Demopoulos, 1962; Gebre-ab *et al.*, 1978). Three modes of presentation of spastic paraparesis have been described (Ganapathy and Dwivedi, 1961). Most common is a sudden onset in which the affected individual complains of heavy, weakened legs after falling down or awakening from sleep. Some subjects report a subacute onset of walking disability, whereas others experience an insidious progression of spastic paraparesis spanning a period of months. In Asia, the degree of neurological compromise is classified according to the extent of walking difficulty and the need for physical support (Acton, 1922). The large majority walks abnormally but without aid ('no-stick stage'), while others require the use of a single stick fashioned from a branch ('one-stick stage') or, less often, a pair of sticks for bilateral support ('two-stick stage'). Rarely, very severely affected individuals develop advanced spastic paraplegia and, in the absence of modern ambulatory aids, are forced to move around on hands and knees ('crawler stage'). An unknown number of subjects appears to stabilize in a subclinical, asymptomatic stage of lathyrism with minimal neurological dysfunction. The disorder has rarely been subjected to contemporary methods of clinical investigation, and there has been no reproducible animal model of spastic paraparesis induced by oral intake of *Lathyrus sativus* (LS) (Spencer and Schaumburg, 1983).

This paper is the first of a number of clinical and experimental laboratory studies designed to illuminate the aetiology and pathogenesis of lathyrism and certain other human motor neuron diseases. Subsequent publications will report the development of a primate model of lathyrism (P. S. Spencer, D. N. Roy, A. Ludolph, J. Hugon, M. P. Dwivedi and H. H. Schaumburg, to be published) and address the role of beta-N-oxalylamino-L-alanine (BOAA), a free 'excitotoxic' amino acid present in *LS* and other *Lathyrus* species that epidemiological studies have suggested is causally associated with human lathyrism (Roy, 1981).

Previous clinical reports of lathyrism generally have not attempted to compare the semeiology of cases from various parts of the world (*see* Gardner and Sakiewicz, 1963; Cohn and Streifler, 1981). In addition to this approach, the present study considers the possible relationship between the amount of *LS* seed (peas) consumed, the mode of clinical presentation, the nature and degree of reversibility of initial clinical manifestations, and the relationship between these factors and the eventual degree of spastic paraparesis.

INDIAN CASES

History and Background

Our initial studies in October 1981 took place in Unnao Province, near Kanpur, Uttar Pradesh (fig. 1), a region of India periodically stricken by flood. Eleven male subjects were interviewed (P.S.S.), examined neurologically (H.H.S.), and their gait recorded on film. Subjects were poor, indigent and minimally nourished villagers who rely on *LS* (locally known as *matri dal*) to prepare soup and bread (*chapati*), the principal constituents of their daily diet. During flood, when other food crops are destroyed, *LS* comprises the major part of their diet. Under such circumstances, many of the subjects developed difficulty walking in 1975.

The following information is drawn from an unpublished survey conducted by local investigators shortly after this lathyrism outbreak. The survey included

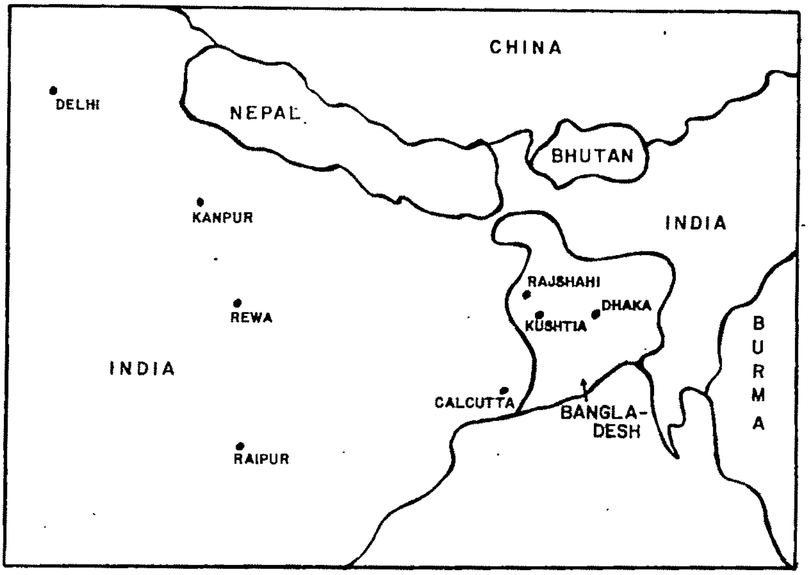

FIG. 1. Location of regions under study in India and Bangladesh.

7 villages, yielding 35 cases (26 adults, 9 children) of spastic paraparesis and 10 subclinical cases. Affected males predominated over female patients (10:1), although an unstated number of stricken women were reluctant to report to the hospital. Duration of the illness ranged from 2 months to 15 yrs (mean: 3 yrs). Age at onset was 40+ yrs (4%), 21-40 yrs (53%), 10-20 yrs (20%) and below 10 yrs (22%). Early clinical manifestations consisted of clumsiness of gait, stiffness and rigidity of the lower limbs (71.4%), paraesthesiae of the limbs (34%), and urinary hesitancy (5.6%). Difficulty in walking was described as having developed over a period of up to 7 days (3 cases), up to 14 days (13 cases), or over a span of 1-6 months (19 cases). All subjects with lathyrism had eaten *LS* since childhood, and intake varied from 50-200 g per day of the chickling pea. The concentration of BOAA in food samples ranged from 0.12% to 1.84%. No BOAA was found in the food (that included certain types of *dal*) of villages in a neighbouring district (Bara Banki) which was free of subjects with lathyrism. In October 1981, at the time of our follow-up study, most of the 11 subjects with lathyrism thought that *LS* consumption was *not* responsible for their disability and instead related the cause to the 'bad wave' (flood). One individual acknowledged having been told that *matri dal* (*LS*) was dangerous but was unable to accept the concept that food could be toxic. On the contrary, the subjects liked *matri dal* since it 'tasted good' and 'made them strong'. Continued consumption of *LS* by subjects was established on interview, and chickling pea samples were collected from one village in which 20% of male members reportedly developed lathyrism in 1975.

Clinical Profile

Table 1 summarizes the initial symptoms, the developing pattern of weakness, and the results of examination of tendon and cutaneous reflexes. All subjects reported early involvement of the lower limbs and one (Case 5) additionally suffered from heaviness and weakness of the arms. Consistently found was a largely symmetric clinical pattern of pathologically brisk knee and ankle jerks (with or without clonus), crossed adductor responses, and extensor plantar reflexes. There was increased tone on passive stretch of the thigh adductors, quadriceps and gastrocnemius muscles, slight weakness of thigh and foot flexors, and no detectable weakness of thigh extensors. Fasciculation in the upper and lower limbs was not found. Examination of gait revealed a wide spectrum of disability ranging from slight leg stiffness only manifest when running (Case 6) to severe spasticity requiring the use of a pair of crutches for walking (Cases 1, 5, 10). Minimally compromised individuals sometimes displayed a bizarre posture in which the legs were flexed at hip and knee and the torso angled backwards (fig. 2). Those who were markedly affected walked with a weaving or jerking gait, with stiff scissoring legs from adductor spasm, bent at the knees and forced on to their toes because of continuous contraction of the gastrocnemius muscles. With the exception of one individual, who showed slight weakness of wrist extensors, fingers and triceps, strength in the

TABLE 1. INDIAN CASES (1-10: UNNAO, UP; 11-13: REWA/SATNA, MP)

Case	*Age (1983) (yrs)*	*Sex*	*Type of onset**	*Symptoms at onset*	*BJ*	*TJ*	*KJ*	*AJ*	*Extensor plantar responses*	*Crossed adductor response*	*Sticks*
1	40	M	Over 8 days	Heavy legs. Fall	+++	++	Clonus	Clonus	+	Crossed	2
2	34	M	Progressive: 3 to 6 mo.	Stiff, heavy, aching legs	++	+	+++	Clonus	+	Crossed	1
3	41	M	Progressive: 3 mo.	Heavy aching legs, then weak	++	+	+++	++++	+	Crossed	1
4		M	Progressive: 4 to 6 mo.	Heavy aching legs, stiff gait	++	+	+++	+++	+	Crossed	1
5	63	M	Sudden, then weakness	Heavy arms and legs	+++	++	++	++	+	Crossed	2
6	20	M	Progressive: 4 to 6 mo.	Heavy aching legs. No weakness	++	+	+++	+++	+	Crossed ±	SC
7	20	M	Progressive: 9 mo.	Heavy aching legs. Gait abnormal	+	+	+++	+++	+	Crossed	0
8	30 approx.	M	Progressive: 6 mo.	Heavy aching legs. Gait abnormal	+	+	+++	+++	+	Crossed	0
9	30 approx.	M	Progressive: 8 mo.	Heaviness, painful ache in thighs	+	+	+++	++	+	Crossed ±	0
10	60 approx.	M	Sudden (2 wks)	Heaviness, weakness in legs	++	+	Clonus	Clonus	+	Crossed	2
11	26	M	Continuously progressive weakness	Tingling, numbness and stiffness of calf muscles and biceps	+++		Testing impossible	Testing impossible	+	Complete adductor contraction	Crawler
12	7	F	Sudden; crawling by 10 d		+		++	+	+	Crossed	0
13	9	F	Sudden; crawling by 10 d		+		++	+	+	Crossed ±	0

* Onset of weakness; BJ = biceps jerk; TJ = triceps jerk; KJ = knee jerk; AJ = ankle jerks. Sticks = support required for walking. SC = subclinical.

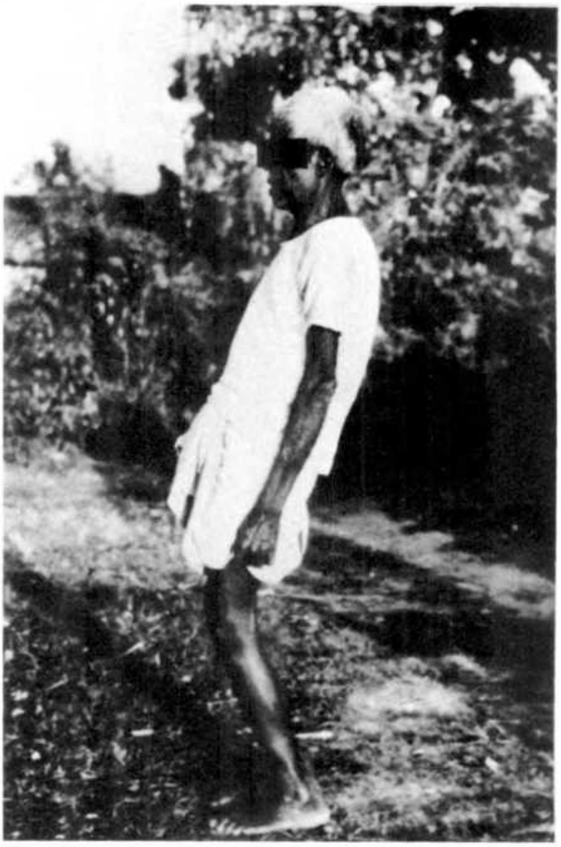

FIG. 2. Minimally affected individual ('no-stick' stage). Spasm of the knee flexors results in an unusual posture commonly seen in early lathyrism. Rewa, MP, India, 1984.

arms was normal. Two subjects displayed brisk tendon reflexes in the upper limbs. The cranial nerves, and cerebellar, bladder and bowel function, were normal, and sensation was intact. An essentially identical neurological picture with no progression was found on re-examination (P.S.S.) of selected individuals in 1983.

Ten additional Indian subjects with lathyrism (7 male, 3 female), drawn from the Rewa division of Satna, Madhya Pradesh (fig. 1), an area subject to cyclical drought, were examined (M.P.D., P.S.S.) and videotaped in their respective villages in February 1984. These subjects are included in an epidemiological survey of lathyrism in this region of India to be reported elsewhere. For illustrative purposes, Table 1 incorporates the findings from a young man (Case 11) with advanced lathyrism (crawler stage) and from 2 young sisters (Cases 12, 13), each with a two-year history of a mildly spastic gait following a large intake of *LS*. Increased tone in the thigh adductors in these girls was unmasked when their knees were observed to touch as they ran. In 1984, other male and female subjects with lathyrism were examined (M.P.D., P.S.S.) in Raipur, MP (fig. 1) and found to have the characteristic clinical features of this disease.

BANGLADESHI CASES

History and Background

Acute food shortages and increasing dependence on *LS* seed as a source of nourishment were causal factors of a major epidemic of lathyrism in NW Bangladesh during 1972 and in the years immediately thereafter. A nonmedical survey of two affected districts, Rajshahi and Kushtia (fig. 1), revealed 10,796 individuals suffering from overt lathyrism (i.e., with an obvious walking difficulty) (Kaul and Islam, 1982; Anonymous, undated).

In June 1985, 17 male subjects with lathyrism (preselected by local health paraprofessionals) were individually interviewed by a local physician with the aid of a standardized questionnaire prepared in Bengali. This was designed to identify causes of paraparesis other than *LS*, the presence of walking disability in other family members, the date of onset, sequence of symptoms, evolution of the disease and the proportion of *LS* consumed before, and after, the onset of spastic paraparesis. Each subject was then examined neurologically (A.L., J.H., P.S.S.). Gait and abnormal neurological findings were videotaped with the informed consent of the subject.

Most (12) subjects developed lathyrism during the famine of 1972 (*see* Mannan, 1985), 3 in 1973, 1 in 1974 and 1 in 1976. Mean age at onset of walking difficulty was 20 yrs (age range: 7–44 yrs). Age at examination was 18–55 yrs (mean: 31.5 yrs). Seven subjects reported a similar disability in up to 3 other family members, and clinical examination of 1 member considered unaffected by the family revealed subclinical ('latent') lathyrism. This subject (Case 25) was included in the case load. Affected family members usually developed walking difficulty approximately at the same time. Past medical histories revealed no birth, head or back trauma, and no significant medical problems other than lathyrism. All subjects consumed *LS* before the onset of their disability and, in the year preceding onset, 13 reported a heavy consumption of *LS*, and 4 a smaller amount. Most of the *LS* (*khesari*) was eaten in the form of *chapati* thrice daily (Mannan, 1985). (Samples of *LS* seeds were not available for analysis.) Other foodstuffs used during a one-year period prior to the onset of lathyrism included wheat/grain seed (16 subjects), rice (12), vegetables (6) and occasional meat or fish (4).

Clinical Profile

Difficulty in walking commenced suddenly in 5 subjects, within a one-week period in another 5; 2 developed difficulty walking over a period of one month, and 4 reported a gradual onset. Six subjects continued eating *LS* after the disease had begun: 2 consumed less *LS*, and 4 ate the same amount as before; 11 denied further *LS* consumption.

Characterization of the early symptoms in the subjects was variable (Table 2). Most commonly, subjects mentioned cramping in calves and/or legs and a sensation of weakness and/or heaviness of the legs. Weakness of the legs always followed

TABLE 2. BANGLADESHI CASES: SYMPTOMS AT ONSET

Weakness, heaviness, or stiffness, both legs	11
Pains and cramps in legs*	6
Fever*	6
Diffuse pain and cramps*	2
Fall	1
Unsteadiness	1
Paraesthesiae in legs*	1
Paraesthesiae* (electric shock)	1
Tremulousness*	1
Urgency*	1
Impotence*	1
Sphincteric spasm*	1
Abnormal thirst	1

* Disappeared after onset of lathyrism.

cramps in the calves or legs, the appearance of the two being separated by periods of 5/7 days to 4 months. Cramps of calves/legs at onset were not experienced by 9 subjects. Seven subjects reported their walking disability had lessened after onset, 2 mentioned increased difficulty, and the remainder experienced no change. There was no apparent correlation between those whose symptomatology changed and the continued consumption of *LS*. Findings on examination in 1985 are shown in Table 3.

Clinical signs of overt malnourishment were absent in all cases. Neurological findings in all subjects were dominated by a spastic paraparesis of the lower limbs. Gait was characterized in the 9 mildly affected ('no stick') cases by restricted movement at ankle and knee causing the subject to walk with a stiff-legged gait, sometimes bent at the knees. The more severely affected had spasm of thigh adductor and gastrocnemius muscles, forcing them to walk on the balls of their feet with a characteristic cross-legged gait. Some required support from a single stick (6 subjects) (fig. 3), others a pair (2 subjects). Bladder and bowel function was affected in none.

Examination of the cranial nerves was unremarkable. Except for 2 subjects (1-stick and 2-stick cases) with, respectively, unilateral or bilateral horizontal nystagmus, cerebellar and sensory signs were absent. All subjects presented unequivocal signs of pyramidal-tract involvement including exaggerated knee jerks with or without patellar clonus, brisk ankle jerks with sustained ankle clonus (induced, in mild cases, by exercise), and extensor plantar reflexes. Pyramidal signs were usually symmetric, although they were asymmetric in some mildly affected cases. No subject showed signs of pyramidal involvement in the upper limbs. Abdominal reflexes were present in 15 of 17. Cremasteric and anal reflexes were preserved, even in the severely compromised. Weakness was restricted to the lower extremities: a variable loss of strength (0–4/5) was found in the thigh abductor and extensor muscles of the foot.

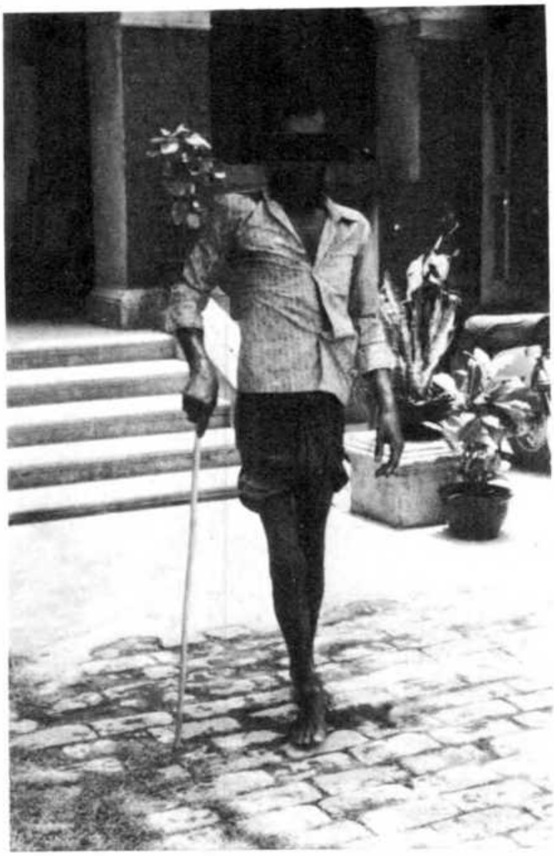

FIG. 3. Subject with a moderate degree of spastic paraparesis and a mildly scissoring gait ('one-stick' stage). Rajshahi, Bangladesh, 1985.

Additionally, in some patients, there was mild weakness of the quadriceps. Tone of the gastrocnemius and thigh adductor muscles was markedly increased. Muscle tone was sometimes increased at the end of limb movement, and clasp-knife responses were also found.

Mannan (1985), who examined 12 subjects from one of the same districts (Kushtia) at the time of the 1972 epidemic, reported that samples of CSF were normal. Serum protein ranged from 70 to 82 g/l; haemoglobin levels varied from 4.2 to 7.5 g/l, indicating the presence of anaemia in all subjects examined.

Individual Case Descriptions (India and Bangladesh)

The following cases illustrate the range of initial complaints and deficit at examination (*see* Table 3). Case reports are ordered to reflect an increasing degree of neurological impairment. The case numbers refer to the listings in Tables 1 and 3.

Case 25: male aged 18 yrs (approximately 5 yrs at onset). Considered normal by family and friends, he was invited for examination because his brother and father were victims of lathyrism. On questioning, his only neurological complaint was a slight stiffness or heaviness of the legs when walking, a sensation that had commenced sometime between 1972 and 1973. Examination in June 1985 revealed

TABLE 3. BANGLADESHI CASES: FINDINGS ON EXAMINATION

Case	*Stage*	*Age (1985) (yrs)*	*Course*	*Principal symptoms at onset*	*Eating habits**	*BJ*	*TJ*	*KJ*	*AJ*$^{++}$	*Extensor plantar responses*
14	2	30	Gradual, 1 mo.	Leg weakness, fever	Large/C	++	++	Clonus	Clonus	+ Unilateral
15	0	40	Progressive, 1 wk	Pain, cramps	Large/C	++	++	++++	Clonus	+ Unilateral
16	1	28	Sudden	Cramps, weakness	Large/C	++	++	++++	Clonus	+
17	1	30	Sudden	Leg cramps	Large/S	++	++	++++	Clonus	+
18	0	50	Sudden	Leg weakness	Large/S	++	++	++++	++++	0
19	1	24	Sudden	Leg cramps	Large/C	++	++	++++	Clonus	+
20	1	40	Gradual, mo.	Leg weakness	Large/C	++	++	Clonus	Clonus	0
21	0	28	Gradual, mo.	Leg pain and muscle spasms	Large/C	++	++	++++	Clonus	+
22	0	26	Sudden	Leg heaviness	Small/S	++	++	++++	Clonus	+
23	0	20	Gradual, 1 mo.	Leg weakness	Large/S	++	+++	++++	Clonus	+
24	0	22	Gradual, 4 mo.	Leg cramps	Large/S	++	+++	++++	Clonus	+
25	0	18	Gradual, wks	Leg stiffness, heaviness	Small/S	++	++	+++	+++	+
26	1	30	Gradual, 2 mo.	Leg stiffness, heaviness	Large/S	++	++	Clonus	Clonus	+
27	0	35	Sudden	Leg weakness	Large/S	++	++	Clonus	Clonus	+
28	0	23	Sudden	Leg weakness	Small/S	++	++	++++	Clonus	+
29	1	55	Gradual, 1 wk	Leg weakness	Small/S	++	++	++++	++++	+
30	2	40	Sudden	Leg weakness	Large/S	++	++	++++	Clonus	+

* C = continued eating *LS* after onset; $^{+}$ least affected ('subclinical') case; S = stopped eating *LS* after onset; $^{++}$ mildly affected cases tested before/after exercise. *See* Table 1 legend for other abbreviations.

pathologically brisk knee and ankle jerks (2–5 beats after exercise) and equivocally extensor plantar responses.

Case 18: male aged 50 yrs (37 at onset). In July, 1972, after heavy consumption of *LS*, he suddenly noticed weakness of his legs after bathing in the river. Cramps and other manifestations of lathyrism at the onset were absent. After reaching home (on a buffalo), he became bedridden for two months during which he received treatment with vitamin B complex. Walking ability recovered and he discontinued eating *LS*. Examination thirteen years later revealed a 'no-stick' case with crossed adductor responses, exaggerated patellar reflexes, brisk ankle jerks with clonus on the right, and spasm of the calf muscles. There was no weakness of the lower limbs and the plantar reflexes were not extensor.

Case 15: male aged 40 yrs (27 at onset). In 1972, after subsistence of *LS* for 1 to 1½ months, he noticed pain and cramps in the calf muscles, especially at night. Sensations akin to electric shocks were experienced in the lower limbs, mostly ascending and sometimes descending. Urgency of micturition, impotence and anal sphincteric spasm were recalled. All these symptoms remained for 5 to 7 days before the subject noted weakness, tremulousness and unsteadiness on standing. Intramuscular vitamin B12 was administered from the outset. Thereafter, weakness gradually developed in the legs until he stabilized as a 'no-stick' case. He continued to eat a smaller amount of *LS*. Examination in June 1985 revealed an asymmetric spastic paraparesis with pathologically brisk knee jerks and sustained ankle clonus, a right extensor plantar response, increased muscle tone of the right adductor muscles and a clasp-knife reflex on flexion of the right knee. Gait was mildly spastic without scissoring.

Case 17: male aged 30 yrs (17 at onset). Some time in 1972, during which he consumed a large quantity of *LS*, the subject developed 'fever and chills' for one day, leaving him bedridden. He noted painful cramping and paraesthesiae in the legs; these symptoms disappeared subsequently. Leg weakness was so severe that support was required. He stopped eating *LS* and stabilized with a disability that required the use of a stick. In June 1985, the subject walked with a spastic scissoring and lurching gait. Examination showed bilaterally exaggerated tendon reflexes with sustained ankle clonus and extensor plantar responses. Muscle spasm was evident in adductor and gastrocnemius muscles, and weakness of foot extensors and quadriceps was present. Abdominal reflexes were intact.

Case 30: male aged 40 yrs (27–28 at onset). After consuming a large amount of *LS* during 1972 and 1973, he fell to the ground unable to support himself while working in the field. Leg weakness gradually increased but other symptoms (Table 2), including excessive thirst, disappeared. After one month, he required one stick to walk; subsequently, two sticks. Examination in June 1985 revealed a severely impaired individual with a spastic gait, brisk knee jerks, crossed adductor reflexes, sustained ankle clonus, and extensor plantar responses. Muscle power was reduced in the lower extremities: foot extensors (0–1), toe extensors (0–1), adductors (3). Sensory signs were absent.

Case 1: male aged 40 yrs (17 at onset). Before the onset of walking difficulty, he had been extremely fond of *dal* and ate more than his brothers who reportedly had been spared the disease. He continued to consume large amounts of *dal* until 1960; more recently his intake of *LS* had diminished and he had discontinued consumption of *LS* in *chapati*. One brother was examined and found to be neurologically intact. The father also walked normally but his wife (who was not available for interview or examination) was alleged to have developed a walking disorder when aged 42 yrs, shortly after her son succumbed to lathyrism.

He fell off his cycle into flood water, climbed out, noted that his legs felt heavy and walked home. Subsequently his legs 'trembled' and became progressively weak, maximum weakness occurring after eight days when he required two sticks to walk. Weight loss was not noted. Onset of weakness was unaccompanied by pain, paraesthesiae, bladder dysfunction or loss of potency, or other disturbances of sexual function. Since the onset in 1958, he reported only slight improvement in his ability to walk. In 1981, he was unable to stand without two under-arm crutches, and walking was accomplished on the toes (gastrocnemius spasm) with an extreme degree of leg scissoring (thigh adductor spasm). Examination then revealed a fairly well-nourished individual with normal mental status, cranial nerve and cerebellar function. Strength of hip and foot flexors was diminished without atrophy, fasciculation or contracture; muscle power in leg extensors and of the upper limbs was normal. Tendon and other reflexes were abnormal in all four limbs. Biceps jerks were pathologically increased and Hoffman signs were present bilaterally. Tapping the tendon of the quadriceps femoris muscles elicited sustained clonus of the entire limb bilaterally. Ankle clonus was also sustained, and extensor plantar reflexes were readily obtained. Sensory examination was normal. An identical clinical picture was found on re-examination of this individual two years later.

Case 5: male aged 63 yrs (55 at onset). After a period of heavy *LS* consumption, he fell while walking through flood water, picked himself up and discovered that his legs and arms felt heavy. Over the following three months, his legs and hands became weak. Subsequently he was stable, used a stick to walk, but was unable to dress or feed himself. Examination in 1981 revealed no clinical signs of overt malnourishment. There was no history of urinary problems, impotence or paraesthesiae. Barefoot gait was slow, deliberate and stiff-legged, with mild rocking of the pelvis. There was a pyramidal pattern of mild to moderate weakness in arms and legs (without atrophy or fasciculation), extensor plantar responses, and exaggerated brachioradialis and biceps reflexes. Corticobulbar and segmental signs were absent, examination of cranial nerves was unremarkable, and the snout reflex was negative. Coordination was generally good and Romberg's sign was absent, although rapid arm movements were deliberate and slow, and the subject buttoned his shirt with great difficulty. Sensation was intact except for a possible mild loss to pinprick on the thickened soles of the feet.

Case 11: male aged 26 yrs (19 at onset). This subject continuously used *LS* as a staple item of diet since no one had informed him of its potentially harmful effects. Onset was marked by tingling and numbness in the legs, and stiffness in the calf muscles and biceps. Bowel and bladder function reportedly were normal at the beginning of the disease, during its course and on examination in 1984. Six months after commencement of lathyrism, he experienced pain and tenderness in his lower limbs; by three years, he required two sticks to walk. At the time of examination, six or seven years after commencement of the disorder, he displayed a spastic paraplegia and moved around on his rump (fig. 4). His torso and arms were very well developed, cranial-nerve function was unremarkable, and the palmomental sign was absent bilaterally. Muscle power in the arms was normal in contrast to the legs where atrophy was marked, and voluntary movement was confined to slight movement of toe extensors and knee flexors.

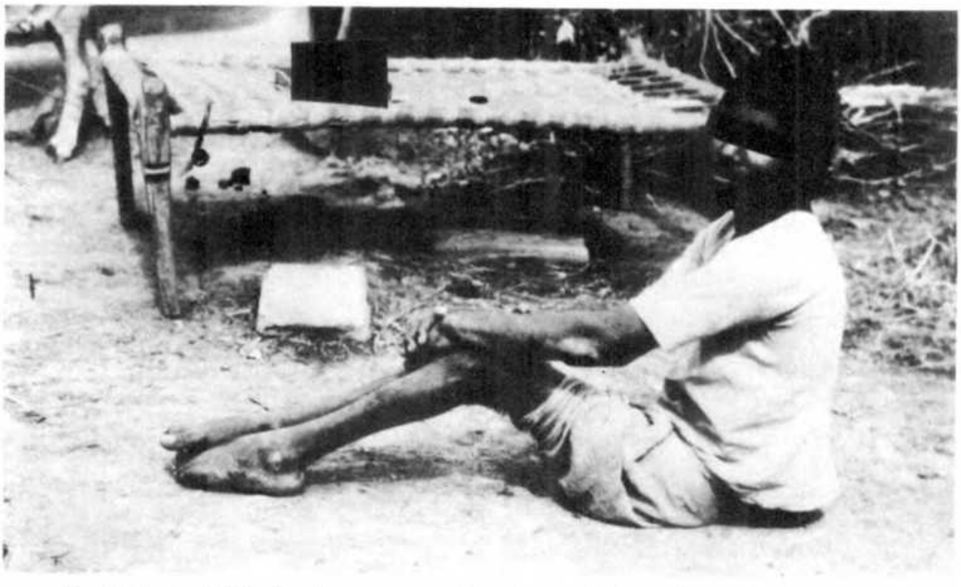

FIG. 4. Advanced lathyrism in a young man ('crawler stage'). Satna district, MP, India, 1984.

The legs were crossed and locked because of contracture of thigh adductors, hamstrings and gastrocnemius muscles. Fasciculation was absent, and sensory examination for pin, brush, vibration and proprioception was normal. Tendon reflexes could not be elicited in the legs which, when the subject was sitting, were in a continuous state of clonus that vibrated the entire body. The plantar reflexes were extensor, and the Hoffmann sign was present. Abdominal reflexes were absent, biceps jerks were very brisk, and the brachioradialis reflexes were exaggerated.

DISCUSSION

Established cases of lathyrism drawn from four regions of the Indian subcontinent (fig. 1) present a remarkably stereotyped clinical picture of varying degrees of spastic paraparesis following a history of excessive consumption of *LS*. These findings are consistent with previous reports demonstrating a strong epidemiological relationship between heavy intake of *LS* and the development of lathyrism (e.g., Ganapathy and Dwivedi, 1961). The most direct evidence of this relationship comes from the experience of European prisoners in the Second World War (Kessler, 1947; Mertens, 1947). One group developed lathyrism after consuming daily 400 g of *LS* peas cooked in salt water, plus 200 g of bread made from barley (80%) and chopped straw (20%) (Kessler, 1947). This epidemic commenced on September 16, 1942, when approximately 1200 Romanian Jews, aged 14–25 years, were interned in a forced labour camp in the Ukranian town of Wapniarka, near the present Romanian-Russian border. A total of 680 poorly nourished people was transferred from prison or other labour camps, and 500 were taken from their homes. Beginning on December 29, 1942, there was a monophasic outbreak of lathyrism involving approximately 800 inmates, mostly among the malnourished, but also affecting those who had been taken from their homes in good health. The first cases of lathyrism to appear were among those who ate their full daily ration and sometimes more. Other prisoners who were provided with daily rations of 200 g of *LS* and 200 g of bread failed to develop lathyrism. Some prisoners possibly suffered from ergotism or an admixture of lathyrism and ergotism, diseases that have coexisted earlier in human history (Gardner and Sakiewicz, 1963). Once the cause of the epidemic was recognized and consumption of *LS* discontinued, no new cases appeared. After the war, many of these lathyrism victims moved to Israel where more than 200 cases have been followed by Cohn and Streifler (1981). Our (H.H.S., P.S.S.) interview and examination of 5 of these male subjects, 39 years after onset of their spastic paraparesis, revealed a pattern of neurological deficit essentially identical to that seen in the 38 subjects studied on the Indian subcontinent. Affected Israeli subjects walked on the balls of their feet with a stiff-legged, scissoring gait and required a cane for support. All displayed extreme spastic resistance to stretch of lower limb muscles, hyperreflexia at the knees and ankles, absent abdominal reflexes and extensor plantar responses. There was no atrophy, skin or hair changes in the legs, and skin temperature was normal. Sensation was normal to touch, pin, cold, position and tuning fork. Two of the 5 complained of urinary frequency but noted that this problem had improved markedly since onset when all experienced severe urinary frequency and urgency. Other victims of lathyrism experienced bladder cramping (Cohn and Streifler, 1981).

On the basis of these observations from Israel and Asia, it can be concluded that lathyrism is a stereotyped, self-limiting neurotoxic disorder found in adequately nourished and undernourished individuals who consume 200–400 g per day of *LS* for periods of one to three months. Even shorter periods of consumption of *LS* have precipitated the disease (Paissios and Demopoulos, 1962). Kessler (1947) suggested that an increased intake of *LS* led to a more severe acute onset that presented earlier than in other, less compromised, individuals who had consumed smaller amounts of *LS*. Adults in the present study who developed the disorder suddenly often had the greatest clinical deficit on examination some years later. By contrast, the 2 young Indian girls who were severely weakened at onset stabilized with only a mild spastic gait.

The clinical picture of lathyrism is dominated by a spastic paraparesis in which the outstanding feature of established cases is greatly increased extensor muscle tone in the lower limbs involving the quadriceps and gastrocnemius muscles. This results in a toe-walking, scissoring, unsteady gait. The tendon reflexes are always pathologically increased in the lower extremities, and ankle clonus, crossed adductor responses and a variety of abnormal superficial reflexes are typically elicited. Tendon reflexes cannot be demonstrated in the lower limbs when a full spastic paraplegia is evident (crawler stage) because of contracture of affected muscles. Pyramidal signs are sometimes found in the arms in the more severely affected; motor weakness of the upper extremities is extremely rare. Atrophy of the lower limbs is largely commensurate with disuse.

This stereotyped clinical picture of spastic paraparesis is consistent with the sparse neuropathological evidence of degeneration of Betz cells and of anterior and dorsolateral corticospinal tracts in thoracic, lumbar and sacral regions of the spinal cord (Buzzard and Greenfield, 1921; Filiminoff, 1926; Ganapathy and Dwivedi, 1961; Sachdev *et al.*, 1969; Streifler *et al.*, 1977). The predominant clinical involvement of the lower extremities in established cases suggests that pyramidal tracts regulating motor function of the legs are affected first, or to a greater proportional extent, than shorter pyramidal tracts subserving movement of the arms. Clinical evidence of a lower motor neuron deficit was absent in most established Asian cases, although distal weakness and marked atrophy of foot extensors were found on occasion. Additionally, Cohn and Streifler (1981) have presented clinical evidence of lower motor neuron dysfunction supplementing the usual clinical picture of lathyrism in 7% of their 200 European cases. Post-mortem histological examination of the spinal cord of one Israeli case revealed cytoplasmic changes but no loss of anterior horn cells (Hirano *et al.*, 1976). Mertens (1947) also argued strongly that a distal motor neuropathy follows shortly after the onset of spastic paraparesis in some severely affected individuals. Concurrent malnutrition as a precipitant of peripheral neuropathy cannot be excluded, nor can the possibility that malnourishment is a susceptibility factor for lathyrism. Malnutrition was present in the Bangladesh epidemic (Kaul and Islam, 1982), although one account of 12 cases examined at the height of the epidemic reported that these patients were 'fairly well nourished' (Mannan, 1985). Detailed studies of nutritional status at the onset of lathyrism are required to clarify this unresolved issue.

The initial clinical manifestations of lathyrism commonly precede the development of leg weakness and seem to wane or disappear once intake of *LS* is reduced or abandoned (*see also* Kojevnikoff, 1894; Kessler, 1947; Cohn and Streifler, 1981). Concurrently, there is often an early improvement in limb strength which is sometimes substantial. This is a spontaneous feature of the disease process and causally unassociated with therapeutic intervention. Early and commonly reversible symptoms of global muscle cramping, urgency and frequency of micturition, nocturnal erection and ejaculation (present data, and Mertens, 1947; Cohn and Streifler, 1981), suggest that *LS* consumption can result in diffuse and transitory CNS excitation of somatic motor and autonomic function. These events seem to be associated mostly with individuals (such as the Israeli cases) consuming a large amount of *LS*. Acutely toxic levels of BOAA, a compound with potent excitatory properties in laboratory animals (Watkins *et al.*, 1966), might account for these phenomena. On the other hand, the presence of urinary dribbling and hesitation in some patients, and the common reports of perverse sensations in affected limbs, suggest early involvement of the primary sensory neuron and/or associated pathways. Sensory neuropathy was not clinically evident in any established cases, although a previous neuropathological report demonstrated some distal degeneration of the gracile tracts (Streifler *et al.*, 1977). The distal sensory neuropathy reported by Cohn and Streifler (1981) in 12/200 Israeli patients could not be demonstrated clinically in any Asian subjects examined in this study. Some of the other rarely reported presenting symptoms (e.g., sleepiness, dreaming, excessive thirst, myoclonic-like movements) implicate involvement of higher centres and could be related to the experimental excitant properties of *LS* extract and BOAA (Roy *et al.*, 1963; Murti *et al.*, 1964; Rao *et al.*, 1964; Olney *et al.*, 1976). These ideas should be tempered with some caution since other acutely neurotoxic species (e.g., *Vicia sativa*) may be harvested and consumed along with *LS* seed (Anderson *et al.*, 1925). Significant ergot contamination of food also may be present on occasion (Kessler, 1947).

Once the presenting symptoms of lathyrism have subsided, the individual may be left with varying degrees of spastic paraparesis indicative of permanent dysfunction of selected regions of the pyramidal system. The neurotoxin(s) in *LS* responsible for this irreversible damage has yet to be identified. Extracts of *LS* and BOAA are known to induce various types of limb paralysis in animals exposed intrathecally (Rao *et al.*, 1967; Chase *et al.*, 1985), but no clear experimental evidence has been presented to demonstrate that prolonged oral intake of *LS* or BOAA induces spastic paraparesis (Spencer and Schaumburg, 1983). The suggestion that BOAA is the culpable agent responsible for the characteristic pyramidal disorder of lathyrism therefore requires further investigation.

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IS THE HEMISPATIAL DEFICIT PRODUCED BY RIGHT PARIETAL LOBE DAMAGE ASSOCIATED WITH RETINAL OR GRAVITATIONAL COORDINATES?

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SUMMARY

The hypothesis that right posterior parietal lesions cause two attentional deficits, namely, a reduced reactivity to stimuli in the left visual field (LVF), and a reduced reactivity to any stimulus which occupies a relative left position, was tested in 8 patients with an extinction syndrome.

In Experiments 1 and 2 the first hypothesis was tested by measuring reaction times (RTs) to visual stimuli presented in the LVF and in the RVF, whereas the second hypothesis was tested by measuring RTs to stimuli totally positioned in the LVF, and in the RVF. The results showed that (1) RTs to stimuli which occupied a relative left position were longer than RTs to stimuli which occupied a relative right position, independent of the visual field stimulated and (2) RTs to LVF stimuli were longer than RTs to RVF stimuli.

Experiment 3 was designed to examine whether the attentional deficit associated with right parietal damage was mostly related to the use of gravitational rather than to retinal coordinates. In this experiment the patients tilted the head either to the left or the right by 90 deg and they responded to two stimuli displayed above and on either side of a fixation mark. The results showed that the difficulty in attending to the left was related both to the gravitational and the retinal frames of reference.

INTRODUCTION

Patients with right posterior parietal injury may fail to respond to stimuli contralateral to their lesion when both sides of space are stimulated simultaneously (for review, *see* De Renzi, 1982). This phenomenon has been termed 'extinction' because typically, it is only obtained under conditions of competitive stimulation; when a single stimulus is presented to the left of the body midline, patients have no difficulty reporting its occurrence. One longstanding explanation of extinction is that it is a disorder of attention, and recent studies have argued that the nature of this attentional deficit specifically involves the orienting component of attention (Riddoch and Humphreys, 1983; Posner *et al.*, 1984; Baynes *et al.*, 1986). These authors reported that, if a patient with extinction is instructed to attend to the

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impaired hemifield, detection of stimuli in this field is only slightly worse than that of stimuli presented in the intact field. In short, the reduced ability to orientate attention towards the left visual field (LVF) can be counteracted to some degree by voluntary control.

The present studies investigated whether the reduced responsivity to 'left' visual stimuli that characterizes the extinction syndrome from right parietal lesions is strictly tied to retinotopic coordinates. Indirect evidence that this may not be the case comes from a study of right brain-damaged patients with left hemi-inattention (Bisiach and Luzzatti, 1978). These patients were asked to recall the buildings situated on the two sides of the Piazza del Duomo in Milan, imagining in one condition that they face the Duomo and in the other condition that they have turned their backs to it. In both conditions they omitted to mention the buildings placed on their left so that those that were recalled in one condition were neglected immediately afterwards in the other condition. The behaviour of these patients seems to suggest that the deficit is not only restricted to stimuli which fall to the LVF but also to the representation of the external world, and that mental scanning was as impaired as perceptual scanning.

The hypothesis that right parietal lesions cause two attentional deficits, namely, a reduced reactivity to any stimulus which occupies a relative left position, plus a reduced reactivity to stimuli in the LVF can be tested quantitatively by measuring reaction times (RTs) to various constellations of visual stimuli. In Experiments 1 and 2, we recorded RTs to visual stimuli that were presented in one of two horizontally aligned positions either in the LVF or the RVF. We asked whether subjects with right parietal lobe damage would take longer to respond to the stimulus that occupied a relative left position, even when both targets appeared in the RVF.

In Experiment 3, we attempted to distinguish between retinotopic and gravitational frames of reference and to ascertain which of the two frames of reference is disrupted following right parietal disease. In all other studies using attentional priming tasks as a method for assessing disturbances in spatial orientation of directed attention, the two kinds of frame of reference were confounded. When the head is in the normal upright position and the eyes are looking straight ahead, these two frames of reference coincide, what is left and right in one frame of reference is left and right in the other. However, when the head is tilted to the left or right by 90 deg, the two frames of reference no longer coincide: what are left and right in the physical frame of reference are down and up in the retinal frame. Therefore, by simply turning the head to the left or right by 90 deg, the two frames are dissociated and it becomes possible to determine which of the two systems is disturbed following parietal lobe damage. The results reported in the present paper suggest that right parietal lobe damage produces a deficit in directing attention in the gravitational system of coordinates, in addition to the retinal system of coordinates.

GENERAL METHODS

Subjects

A total of 8 patients with CT-confirmed unilateral vascular lesions involving the right parietal lobe (*see* Table) who extinguished to double simultaneous visual stimulation (*see* below) participated in these studies.

All patients were residents of the Burke Rehabilitation Hospital, and none displayed evidence of neglect or of a receptive or expressive language disturbance. The presence/absence of neglect was tested in a task requiring the crossing out of circles symmetrically arranged around a central circle (Bisiach *et al.*, 1979).

TABLE. CLINICAL DATA FOR PATIENTS WHO PARTICIPATED IN EXPERIMENTS 1 AND 3 (CASES 1-5) AND IN EXPERIMENT 2 (CASES 6-8)

Case	*Age (yrs)*	*Sex*	*Hand*	*CT scan*
1	55	M	R	R haemorrhagic infarction of parietal lobe, MCA territory
2	60	F	R	R parietal infarct
3	60	M	R	R parietal infarct
4	70	M	R	R frontoparietal infarct
5	63	F	R	R frontoparietal infarct
6	49	F	R	R middle cerebral artery aneurysm
7	63	F	R	R parietal infarct
8	77	M	R	Haemorrhagic infarction of R posterior frontal and parietal lobe, MCA territory

MCA = middle cerebral artery.

Apparatus

Stimuli were generated by an Apple II microprocessor and displayed on a 15 in video monitor. For experimental trials, a two-button response box was fixed to a table under the subject's right hand and connected to the computer. Subjects pressed the left button with their index finger and the right button with their middle finger. The computer recorded responses and response latencies, and stored these data on a magnetic disc for subsequent analysis. All displays were viewed from a distance of 40 cm under normal room illumination. Subjects' eye movements were monitored by the experimenter throughout the experimental session.

Extinction

Before the experiment, the presence of visual extinction was assessed for each subject. The computer-controlled visual display for this purpose consisted of four right angles (2.5 deg/sides) forming the four corners of an imaginary 12.5 deg/side square around a central fixation point. A trial began with a period of central fixation followed by the presentation of one of three possible stimulus conditions; (1) two X stimuli were briefly displayed, centred in two of the squares; (2) one X was displayed; or (3) no stimuli were presented. A tone was sounded immediately afterwards and the subject was required to indicate, by pointing with the index finger of the right hand, which of the squares had contained an X. Each X subtended 0.6 × 1.2 deg of visual angle and was displayed for 75 ms.

The extinction test consisted of 96 trials: 24 trials in which a single stimulus was presented 6 times in each of the four squares; 48 trials in which two stimuli were presented simultaneously, equally distributed across each of the 6 possible between and within-field combinations; and 24 trials in which no stimulus appeared (catch trials). All patients who participated in the following studies omitted more than 20% of the stimuli on the left on between-field double presentations, whereas they consistently detected single stimuli or between-fields stimuli in the right visual field.

EXPERIMENT 1

Experiment 1 examined whether patients with right parietal lobe damage respond more slowly to stimuli that occupy a relative 'left' position, irrespective of which visual field is stimulated.

Methods

Subjects. Five patients, selected according to the above criteria, participated in Experiment 1.

Conditions and procedure. The experiment comprised three conditions, each of which consisted of a continuously displayed central fixation stimulus and two horizontally aligned 2.5 deg/side squares (*see* fig. 1). The horizontal distance between the centres of the squares was always 9 deg. In Condition 1 (fig. 1A), the squares were displayed symmetrically about the vertical meridian. In Condition 2 (fig. 1B), both squares were displayed in the LVF, with the nearest edge of the rightmost square 9 deg to the left of the fixation stimulus. In Condition 3 (fig. 1C), both squares were displayed in the RVF, with the nearest edge of the leftmost square 9 deg to the right of the fixation stimulus. Thus, when the squares were in the RVF, the one placed 9 deg from the fixation stimulus could be classified as 'left', whereas the one placed 18 deg from fixation could be classified as 'right'. The opposite was true when the squares were displayed in the left visual field.

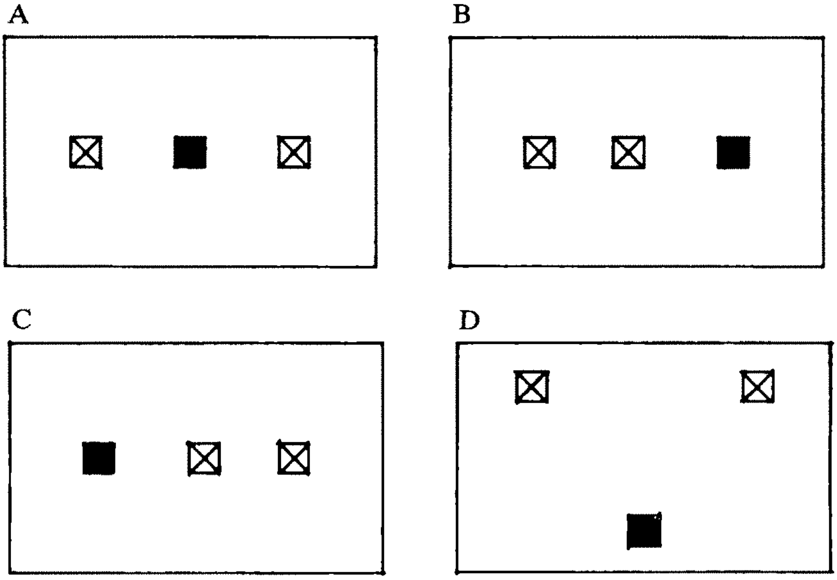

FIG. 1. Stimulus array for: A, LVF and RVF display, B, LVF display; C, RVF display; D, display for head-tilted condition.

Each trial began with the instruction to look at the fixation stimulus. Eye movements were monitored by the experimenter who was situated in front of the patient in an advantageous position for the detection of eye movement. The patient was aware that the experimenter was monitoring eye movements and he/she was instructed to look at the fixation stimulus whenever an eye movement occurred. When accurate fixation was established, the experimenter initiated the trial from the Apple keyboard, a 100 ms variable delay elapsed, and a target X appeared centred in one of the squares for 150 ms. Trials in which eye movements occurred were omitted from the analysis but not replaced. The subject was instructed to push the left response button when the X appeared in the left box, and the right button when it appeared in the right box. In order to avoid any influence of left–right confusion on a subject's performance, instructions were given by pointing to the stimulus to which a given finger had to respond, as well as to the finger itself. The order of conditions for each subject was randomized. RTs were measured from the onset of the stimulus to the appropriate key press.

Each subject attended three experimental sessions that were run on consecutive days. Each session consisted of three blocks (one for each condition) of 30 practice trials and 100 experimental trials per block, with a 20 min rest period between sequences such that left and right target stimuli were equally probable, with the restriction that no more than three consecutive right or left stimuli could occur. The subjects were not aware of the run length restriction.

Results

Only RTs between 100 ms and 1500 ms were included in the analysis. Trials in which reaction times fell within this range, but the subject responded incorrectly or an eye movement occurred, also were omitted from the analysis. Average RTs for each of the three conditions are given in fig. 2.

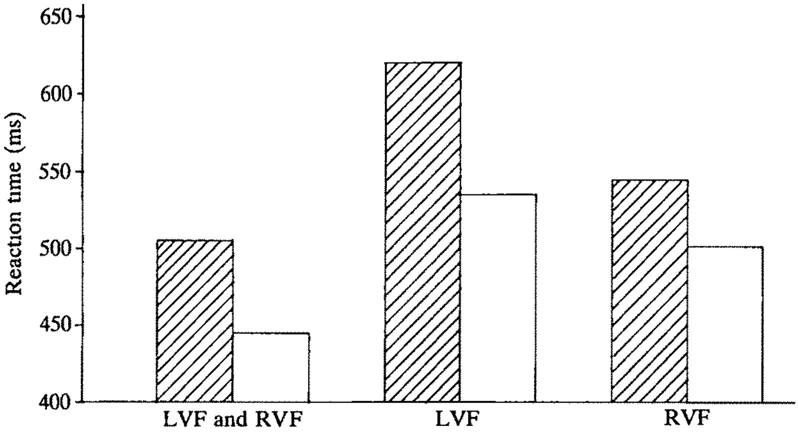

FIG. 2. Reaction times as a function of the stimulus position and the visual field stimulated in head-upright condition (Experiment 1). Left stimulus (hatched areas); right stimulus (open areas).

A preliminary inspection of these data revealed the same general pattern of results for the three conditions: independent of visual field, RTs to the right stimulus were always faster than RTs to the left stimulus. Hence when the two target stimuli were presented to different hemifields (Condition 1), the average RT to the right stimulus (446 ms; SD 121) was 59 ms faster than that to the left stimulus (505 ms; SD 117). Similarly, when both stimuli appeared in the LVF (Condition 2), the difference between RTs to right (535 ms; SD 149) and left (620 ms; SD 165) stimuli was 85 ms. Finally, when they appeared in the RVF (Condition 3), the difference between RTs to right (501 ms; SD 117) and left (544 ms; SD 124) stimuli was 43 ms.

In addition to the effect of stimulus position, an effect of visual field was obtained: RTs for the LVF were slower than RTs for the RVF. Hence, when RTs for the stimulus positions within each visual field are combined, independent of the distinction between left and right stimulus, the average RT for the LVF stimuli is 578 ms, whereas that for the RVF stimuli is 522 ms.

A 3 × 2 analysis of variance with repeated measures using Condition (stimulus presented either to the LVF or to RVF, both to LVF, and both to RVF) and Stimulus Position (left, right) as main factors, revealed a significant main effect of Stimulus Position (F (1,4) = 16.47; $P < 0.025$) with the right stimulus (494 ms) yielding faster RTs than the left stimulus (556 ms). This result was quite reliable across subjects: all subjects responded faster to the right stimulus in all conditions, with the exception of 1 subject who showed a small advantage (14 ms) for the left stimulus in Condition 3.

The other main effect, Condition, was also significant (F (2,8) = 7.02; $P < 0.25$), with Condition 1 (one stimulus was presented to each visual field), yielding the fastest RTs (475 ms), Condition 3 (both stimuli in the RVF) yielding intermediate RTs (522 ms), and Condition 2 (both stimuli in the LVF) yielding the slowest RTs (578 ms). Only the difference between Conditions 1 and 2 was significant (t (4) = 6.27; $P < 0.01$).

Finally, the interaction between Condition and Stimulus Position also was significant (F (2,8) = 5.61; $P < 0.05$). This significant interaction is due to the larger difference between RTs to left and right stimulus in Condition 2 (85 ms) than in Condition 3 (43 ms) (t (4) = 3.90; $P < 0.02$). The difference between the two stimuli is larger in RVF than in LVF, because in the RVF Condition the usual right stimulus advantage is counterweighted by the retinal eccentricity effect, that is, the right stimulus occupies the most eccentric position in the retina.

A similar analysis of variance was carried out on the arc-sine transformations of percentages of correct responses. These data are depicted graphically in fig. 3.

'Incorrect' trials were those in which a response occurred, but RT exceeded 1500 ms and those in which the subject failed to respond, anticipated the target, or pressed the wrong button. The last three types of errors were very rare and did not exceed 3% of the trials. Analysis of the percentage of correct responses yielded a

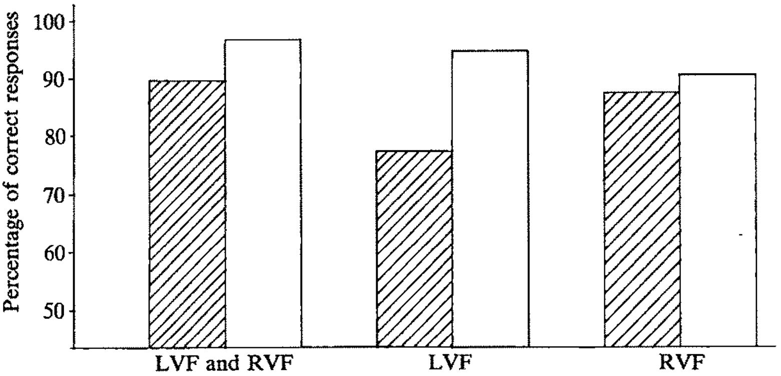

FIG. 3. Percentage of correct responses as a function of stimulus position and visual field stimulated in head-upright condition (Experiment 1). Left stimulus (hatched areas); right stimulus (open areas).

significant main effect only for Stimulus Position (F (1,4) = 21.13; $P < 0.025$), which was due to the difference in accuracy between responses to left and responses to the right stimuli ($P < 0.05$ in all conditions).

Discussion

In accordance with the results of the extinction test, the results of Experiment 1 show that, if a single stimulus is presented to the LVF or to the RVF, patients with extinction can consistently detect it. However, the response latencies to LVF stimuli are longer than those to RVF stimuli.

The most interesting aspect of these results is that, independent of the visual field stimulated, the stimulus that occupies a relative left position yields longer RTs than the one on the right. Hence, even when all stimuli appear in the RVF, subjects respond faster to the right target.

Taken together, the present findings suggest that the changes in responsiveness to visual stimuli associated with right parietal lobe damage are not strictly limited to stimuli appearing in the LVF, but are also present in each visual field when attention has to be divided between two stimuli that can be coded as either 'left' or 'right'.

Since the present experiment employed two horizontally aligned push-buttons and two different fingers, this conclusion can be challenged for several reasons. One possibility is that the index finger, which always responded to the left stimulus, is slower than the middle finger, which always responded to the right stimulus. A second criticism is that the obtained attentional deficit is not related to the left stimulus but, rather, to the choice between the left and the right button. In fact, it is possible to argue that, even though the stimuli and responses were always compatible (i.e., left stimulus was responded to by the index finger which occupied a relative left position and vice versa for the right stimulus that was responded to by the middle finger which occupied a relative right position), the patients had problems in discriminating left from right.

These criticisms were addressed by replicating Experiment 1 in three additional patients except that, instead of measuring choice reaction times, we employed a simple reaction time paradigm in which subjects made the same response irrespective of where a stimulus appeared.

EXPERIMENT 2

Methods

Three patients, selected according to the same criteria as in Experiment 1, participated in this experiment. The apparatus and the procedure were identical to those of Experiment 1, except that subjects were instructed to press the push-button under their index finger upon the appearance of the stimulus, independent of its position in the visual field.

Results

The results reveal that, for both visual fields, the average RTs to the right stimulus (491 ms) were faster than those to the left (560 ms). All subjects showed the same trend in all conditions. In Condition 1, where the stimuli were presented to different visual fields, the average RT to the right stimulus (500 ms; SD 177) was 110 ms faster than that to the left stimulus (610 ms; SD 198). In Condition 2, where both stimuli were presented to LVF, the difference between RTs to the right stimulus (502 ms; SD 163) and those to the left stimulus (583 ms; SD 190) was 81 ms; in Condition 3, where the stimuli were presented to the RVF, the difference between RTs to the left (487 ms; SD 172) and the right stimuli (469 ms; SD 172) was 18 ms. Moreover, as before, RTs to the LVF (542 ms) stimuli were slower than RTs to the RVF (478 ms) stimuli.

A 3×2 analysis of variance with repeated measures using Condition (stimulus presented either to the LVF and to the RVF, both to the LVF, and both to RVF) and Stimulus Position (left, right) as main factors, revealed a significant main effect of Stimulus Position ($F(1,2) = 34.27$; $P < 0.05$) with the right stimulus being 69 ms faster than the left stimulus. Furthermore, the interaction between Condition and Stimulus Position was also significant ($F(2,4) = 7.88$; $P < 0.05$), due to the bigger difference between RTs to left and right stimulus in Condition 2 (81 ms) than in Condition 3 (18 ms) ($t(2) = 4.5$; $P < 0.05$). Also in this experiment the bigger difference between the two stimuli in LVF-Condition than in RVF-Condition is due to a summation of retinal eccentricity effect and the attentional bias for the right spatial position.

A similar analysis of variance was carried out on the arc-sine transformations of percentages of correct responses, but neither the main factors nor the interaction were significant.

Discussion

The results of Experiment 2 clearly demonstrate that damage to the right parietal lobe results in reduced responsivity to stimuli that appear in a relative left position. However, they reveal little about the factors that determine whether a stimulus is coded as ‘left’ or ‘right’. For example, there are at least two spatial codes for describing the position of a stimulus relative to the observer: an environmental, or physical frame of reference, and an egocentric, or retinal frame of reference. When the head is in the normal upright position, these two frames of reference coincide so that what is left and right in one frame of reference is left and right in the other. However, when the subject tilts his/her head, say to the right by 90 deg, the two frames of reference no longer coincide: what are left and right in the physical frame of reference are down and up in the retinal one. Hence, a subject with his or her head rotated can use one of two codes, one egocentric and the other physical, for describing any position in visual space (Attneave and Olson, 1967; Attneave and Reid, 1968; Ladavas and Moscovitch, 1984).

Therefore in an experimental situation in which two stimuli are disposed horizontally above and on either side of a fixation point, and the patient’s head is tilted to the left or to the right by 90 deg, both stimuli fall in the RVF and LVF, respectively, but they can still be coded as ‘left’ and ‘right’ according to gravitational coordinates. Hence, in this condition the patient can adopt one of the two frames of reference for coding the relative positions of the two stimuli.

In this context, if the attentional deficit associated with right parietal lobe damage is only related to the LVF, we would expect no difference between the two stimuli within a condition (with the exception of a little difference due to the upper and lower visual fields), even though in environmental coordinates, one is to the left of the other. The same results should be expected if the attentional deficit is related to the sagittal midplane of the trunk and to the line of sight (body coordinates), as suggested by Bisiach *et al.* (1985), because both stimuli are presented to the left of body coordinates (left hemispace) when the head is tilted to the right and to the right (right hemispace) when the head is tilted to the left. In contrast, if the deficit is related strictly to the use of gravitational coordinates, we would expect slower RTs to the left than to the right stimulus, but no differences between LVF and RVF or left and right hemispace. Finally, if both physical and egocentric frames of references are affected by parietal lobe damage, then we would expect a reduced responsivity to both egocentrically 'left' and gravitationally 'left' stimuli. Experiment 3 was designed to explore these possibilities.

EXPERIMENT 3

In this experiment, the two stimuli were aligned horizontally above and on either side of a fixation mark, and the subject tilted his/her head and the sagittal midplane of the trunk to the left (Condition 4) or to the right (Condition 5) by 90 and 40 deg, respectively. The head rested on a horizontal wooden board. When the head was tilted to the left, the left stimulus was in the upper RVF, and the right stimulus in the lower RVF, whereas when the head was tilted to the right, the association was reversed, so that the left stimulus was in the lower LVF and the right stimulus was in the upper RVF. In both conditions of head tilt, there was a left stimulus and a right stimulus according to the gravitational frame of reference. Hence, Conditions 4 and 5 were very similar to Conditions 2 and 3 of Experiment 1, since in each condition of head tilt both stimuli were in either the right or left visual field. Unlike Experiment 1, however, here the two stimuli were equidistant from the fixation mark.

Methods

The same 5 patients that participated in Experiment 1 served in this experiment. The apparatus and procedure also were the same, except for the position of the two stimuli, which this time were 10 deg on either side of fixation point, and 7 deg above the plane of fixation (*see* fig. 1D).

Results

The general pattern of results, depicted graphically in fig. 4, replicated those of Experiment 1 in that (1) RTs to LVF (598 ms) stimuli were slower than those to RVF (505 ms) stimuli, and (2) RTs to the left (physical) stimulus (593 ms) were slower than RTs to the right (physical) stimulus (510 ms), both in the LVF (Condition 4) and RVF (Condition 5).

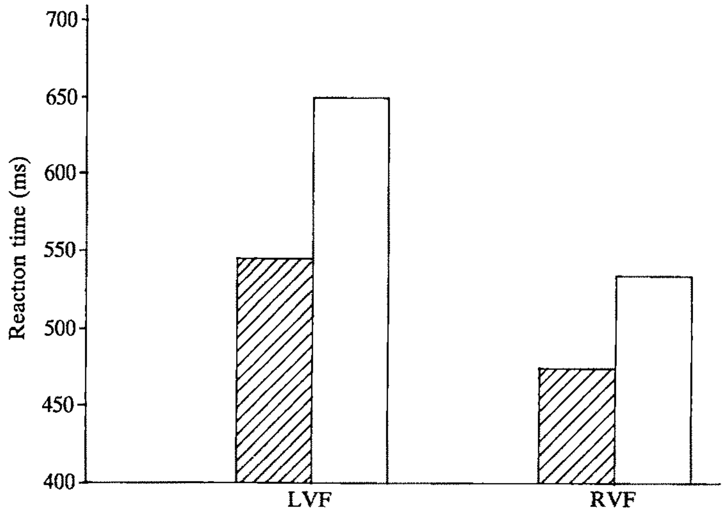

FIG. 4. Reaction times as a function of stimulus position and visual field stimulated in head-tilted condition (Experiment 3). Right stimulus (hatched areas); left stimulus (open areas).

A 2 × 2 analysis of variance using Head Position (right tilted and left tilted) and Stimulus Position (left and right in physical space) as main factors revealed a significant effect of Stimulus Position (F (1,4) = 8.49; $P < 0.05$), reflecting the fact that the right stimulus yielded faster RTs than the left stimulus, both in the LVF (546 ms vs 651 ms) and RVF (475 ms vs 535 ms). All subjects showed the same effect in both conditions. The other main effect, Head Position, also was significant (F (1,4) = 9.28; $P < 0.05$), in that patients responded slower to LVF stimuli (598 ms, right tilted condition) than to RVF stimuli (505 ms, left tilted condition). All subjects showed the same effect. The interaction between Head Position and Stimulus Position was not significant. A similar analysis of variance was carried out on the

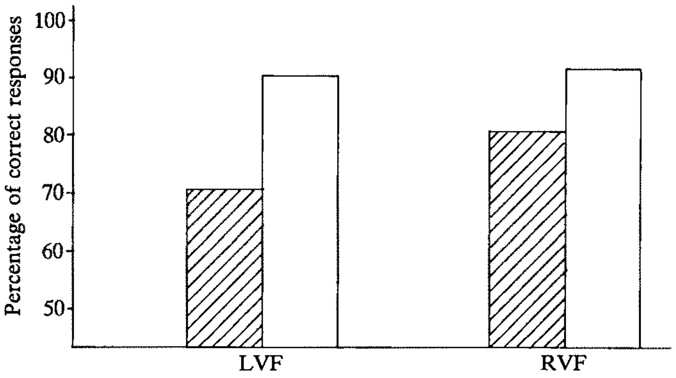

FIG. 5. Percentage of correct responses as a function of stimulus position and visual field stimulated in head-tilted condition (Experiment 3). Left stimulus (hatched areas), right stimulus (open areas).

arc-sine transformation of percentage of 'correct' responses as defined in Experiment 1. These data are graphically depicted in fig. 5.

Only the main effect Stimulus Position was significant (F (1,4) = 70.4; $P < 0.005$), due to fewer errors for stimuli appearing to the right than to the left of fixation (76% vs 91%, respectively). In conclusion, Experiment 3 suggests that the reduced ability to shift attention from one spatial location to another is tied to gravitational coordinates in addition to retinotopic coordinates.

GENERAL DISCUSSION

The present study suggests a number of features about the impaired spatial distribution of attention in patients with the extinction syndrome. The results indicate (1) that patients with right parietal lesions have difficulty responding to stimuli that occupy a leftmost position, no matter which visual field is stimulated, and (2) that the reduced responsivity to 'left' stimuli is related to the gravitational coordinates in addition to the retinal coordinates.

One interesting aspect of the results is that when two stimuli appear in the same visual field, whether right or left, the longest reaction times are always associated with the leftmost stimulus. Furthermore, the responses to a left stimulus are always less accurate than responses to a right stimulus. This finding is in accordance with the clinical observation of patients with the extinction syndrome. Kinsbourne (1977), testing extinction by locating two stimuli in the intact visual half-field of vision (i.e., RVF), found that sometimes the patient attended to the more lateral of the two horizontally adjacent stimuli (i.e., the right stimulus). This observation is not unusual in animals. For example, Lamotte and Acuña (1978) found that monkeys with unilateral posterior lesions showed a misreaching consisting of a deviation toward the side of lesion with either limb, even when the target was in the hemispace ipsilateral to the lesion.

Mesulam (1981) suggested that this deficit may reflect a global attentional bias toward the hemispace ipsilateral to the lesion. The same explanation can account for the reduced responsivity and accuracy to leftmost stimuli obtained in the present study, so that attention is captured by the stimulus ipsilateral to the lesion to such an extent that moving attention from that location towards the left delays responses to any left target. An evidence of this directional preference has also been reported by Kinsbourne (1977). When hemi-inattentive patients were requested to close their eyes and then to open them and to read the full page title of newspaper, they immediately turned to the rightmost end of the title. The same phenomenon has been noted by De Renzi (1982), who observed that if the neglect was not too severe, patients came back to the start of the sentence; otherwise they lingered on the rightmost word, which remained the only one eventually read.

The results in the head-tilted condition add another dimension to the deficit by showing that the difficulty in attending to the left is tied to gravitational coordinates. In all other studies using an attentional-priming task as a method for assessing disturbances in spatial orientation of directed attention, the two frames of reference were confounded. By simple turning of the head by 90 deg, the two different frames of reference are dissociated and it becomes possible to determine which of the two systems is disturbed following parietal lobe damage. The results reported here suggest that right parietal damage produces deficits also in the gravitational system of coordinates. In both conditions of head tilt the gravitational right stimulus yields faster RTs than the gravitational left stimulus.

This finding can be interpreted as a consequence of a different attentional bias of the two hemispheres in physical space. More specifically, even if each hemisphere can attend to any position in space, the right hemisphere is better for attending to the gravitationally left stimulus and the left hemisphere for the gravitationally right stimulus. In this context, we (E. Ladavas *et al.*, unpublished results), using the same head-tilted condition and the same experimental paradigm as in Experiment 3, found that the right hemisphere of split-brain patients, although capable of attending to both stimuli, was more efficient for the left stimulus, and the left hemisphere for the right stimulus.

Therefore the difficulty of right parietal lobe patients to attend to gravitationally left stimuli may occur because these patients are forced by the intact left hemisphere to attend to the right stimulus to such an extent that moving the attention from this location delays the responses to any left target. With brain damage present in the right hemisphere, the attentional system allocates the majority of its resources to the intact hemisphere which then becomes reflected in faster reaction times to stimuli which occupy a right position. If this interpretation is correct, we should expect comparable results after left parietal lesions. The work of Posner *et al.* (1984) suggests that this may be the case.

Finally, the results of the present study indicate that patients with right parietal lesions respond more slowly to LVF stimuli than to RVF stimuli. This result cannot be interpreted in terms of a single explanation. In fact it can be attributed to (1) a different anatomical connectivity of the responding hand with the hemispheric representation of the two visual fields; (2) to an attenuated hemiamblyopia in the visual field contralateral to the lesion; and (3) an imbalance of attention between the two visual fields.

As far as the first explanation is concerned, there is abundant anatomical evidence (Sperry, 1964; Myers, 1965) that the activity of each hand, and its somaesthetic and visual control, are highly lateralized in the opposite hemisphere. As a consequence, the ipsilateral responses (i.e. right hand/RVF stimuli) are always faster than contralateral responses (i.e. right hand/LVF stimuli) (Berlucchi, 1974; Anzola *et al.*, 1977). Because of the hemiplegia in the arm contralateral to the lesion, the patients were forced to respond with their intact, right hand. The right field advantage found in the present study may in principle be accounted for by this anatomical effect, but since such an effect is usually in the order of 2–10 ms, well below the 56 ms (Experiment 1) and the 93 ms (Experiment 3) advantage for the right field found here, this proposal seems untenable.

The second hypothesis, that is, an attenuated hemiamblyopia in the visual field contralateral to the lesion, cannot be evaluated because the patients were not tested for this possible deficit.

Finally, the reduced responsivity to LVF stimuli can be explained by a general attentional deficit which should not be confused with the specific deficit in shifting attention from one spatial location to another, shown by patients with right parietal injury (Posner *et al.*, 1984). In fact, neither in Experiment 1 (Conditions 2 and 3) nor in Experiment 3 did the subject have to shift attention from one visual field to the other, because the presentation of the stimuli was blocked in each condition. Therefore, it is possible that patients with right-sided lesions have especial difficulty in maintaining a high level of alertness and that this is particularly evident for stimuli presented in the visual field directly connected with it. Recently evidence has been accumulated showing that the right hemisphere may be more closely involved in the alerting and in the arousal of cortex by noradrenaline and serotonin than the left hemisphere (for review, *see* Tucker and Williamson, 1984).

The present experiment cannot distinguish between the three hypotheses and further investigations are required in order to clarify the nature of the LVF deficit.

It is commonly believed that the symptom of extinction is associated with a normal reactivity to a single stimulus presented in any part of the visual field. The present experiments show that the reaction time method is sensitive to a left stimulus deficit in patients with right parietal injury, even under conditions in which no competing stimulus is presented. It seems, therefore, that when both spatial positions contain potentially meaningful events of equivalent value, as in the paradigm of bilateral simultaneous stimulation, the right event captures attention to such an extent that the left event is ignored. On the contrary, when the two spatial positions have an equal probability of being stimulated, as in the paradigm used in the present study, the right stimulus is not so salient as to extinguish the left stimulus completely, but it delays the responses to any left target. This may occur because these patients are forced by their intact left hemisphere to attend to the right stimulus, in the absence of full attentional control of the right hemisphere over the left stimulus. In conclusion, the present experiments suggest that the parietal lobe may be organized in shifting attention from one location to another in physical space instead of being redundant apart from possessing retinotopic maps in primary visual cortex.

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MULTIPLE SCLEROSIS IN NORTH-EAST SCOTLAND

AN ASSOCIATION WITH HLA-DQw1

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SUMMARY

This study reports the frequencies of HLA antigens and the polymorphic variants of C4, C2, and Bf for 200 patients with multiple sclerosis (MS) living in the Grampian region of Scotland, an area of high disease prevalence. A group of 128 normal subjects from the same region were typed for comparison. Although the frequencies of HLA-B7 and DR2 in the patient group (43.3% and 49.4%, respectively) were found to be similar to those reported for other Northern European HLA studies on patients with MS, high frequencies of these antigens were also observed in the group of normal Grampian subjects (38.3% and 40.6%) the differences were not statistically significant. However, a significant association was found between the recently defined Class II HLA antigen, DQw1, and MS ($P < 0.006$) when compared with controls. There were no significant differences in frequency of the polymorphisms of C4, C2, and Bf when the group of patients with MS was compared with the control group of normal subjects.

The patients were subdivided according to disease severity, remittent versus progressive clinical course, age of onset of the disease and initial symptoms. The frequencies of the HLA and complement polymorphisms (C4, C2, and Bf) were analysed in these subdivisions. DQw1 was found with similar frequency in severe and benign disease (78% and 80%, respectively) but DR2 was most frequent in the group of patients with remittent disease (54%). There were no significant differences in frequency of the polymorphisms of C4, C2, and Bf between the above subgroups of patients and overall no significant HLA associations were found with age of onset of disease or initial symptoms.

The findings suggest that in an area of high prevalence of MS, the disease is more closely associated with DQw1 than DR2. Furthermore, there was no evidence to support the hypothesis that the HLA region complement gene polymorphisms show significant association with a putative HLA-linked MS susceptibility gene.

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INTRODUCTION

There is now general agreement that both environmental and genetic factors are involved in the aetiology of multiple sclerosis (MS), although the precise nature of each is uncertain. Genes in the HLA region of the sixth chromosome have been repeatedly implicated by the observation of increased frequencies of certain HLA antigens in groups of patients with MS compared with appropriate control populations. The most commonly observed association is with HLA-DR2 in Caucasian populations (*see* reviews by Stewart and Kirk, 1983; Ebers, 1983; McDonald, 1984; Batchelor, 1985; Compston, 1986).

There are, however, discrepancies. In an Arab population an association was found with DR4 (Kurdi *et al.*, 1977) and no association has been indentified in Israelis (Brautbar *et al.*, 1977) or Japanese patients with MS (Naito *et al.*, 1982). It appears that MS is very uncommon in the Gypsies in Hungary amongst whom the incidence of DR2 is very high (Gyódi, *et al.*, 1981; Pálffy, 1982). Finally, in the Caucasian population of the Orkney Islands where the prevalence of MS is the highest recorded, Poskanzer *et al.*, (1980*b*) found no association between MS and DR2 or Dw2. This is the only Northern European/Scandinavian Caucasian population in which an association with DR2 has not been found. It is thus clear that DR2 itself does not confer susceptibility to MS. However, the frequency with which an association is found with genes in the DR region suggests that we should be seeking a gene, or genes, which are in strong linkage disequilibrium with DR2 in a similar population.

The Grampian region of north-east Scotland is of unusual interest, for several reasons. First, it has a high prevalence of MS. A recent study (Downie and Phadke, 1984) has shown a total number of patients in the region of 839 giving a prevalence of 178/100,000 for all cases of MS. Although lower than the prevalence rate of the Orkney and Shetland Islands (Poskanzer *et al.*, 1980*a*) it is certainly the highest reported prevalence in the world for a population of its size (440,000). Secondly, the specialist neurological services are provided by a single major teaching hospital in Aberdeen. About 40% of the population in the region lives within the city and virtually no patients are too remote for referral. In addition, the involvement of one specialist (A.W.D.) in all major studies in this region, to date, had led to a high level of consistency in diagnosis and efficiency of follow-up. A third point of critical importance, in a study of this nature, is the relative stability of the local population and its genetic homogeneity despite the recent advent of the oil industry. Fourthly, its population has some ethnic ties with that of the Orkney Islands and its latitude (57° N) is similar (60° N). Finally, good record systems, diagnostic facilities and close cooperation from the general practices have all contributed to a near complete ascertainment and follow-up of cases involved in this analysis. In this region, therefore, we have attempted to determine the influence that each of the three classes of genes in the MHC (*see* below) has on susceptibility to MS. We have also examined their relationship to disease severity and certain clinical factors such as age at onset, initial symptomatology and clinical course which are known to influence disease progression.

The Major Histocompatibility Complex (MHC)

The MHC region is located on the short arm of chromosome 6 and is divided into 3 classes of genes. Class I genes code for the histocompatibility antigens of the HLA-A, -B, and -C series, and Class II genes code for HLA-DR and HLA-DQ, defined serologically, and HLA-DP, defined by cellular typing (Albert *et al.*, 1984).

At present 16 DR antigens have been clearly defined by cytotoxicity tests on normal B lymphocytes (Albert *et al.*, 1984). The more recently indentified DP and DQ series are also very polymorphic but the full extent of their variation has not been so well defined as is the case for the DR series. It is already clear that the DR and DQ series show a marked degree of linkage disequilibrium, that is, certain alleles of the two series tend to occur in particular combinations more often than would be expected from their individual gene frequencies. HLA-DR2 is known to be in linkage disequilibrium with HLA-DQw1 but there are, at present, no data on the frequency of the serologically determined DQ antigens in patients with MS and their relevant control populations.

The Class III genes code for a group of complement components: C4 and C2 (classical pathway) and Factor B or Bf (alternative pathway). There is limited information concerning the frequencies of Class III polymorphisms in patients with MS, but it is known that Class III genes show linkage disequilibrium with the Class I and II genes (Alper *et al.*, 1984) and interactive influences in MS have been documented (Fielder *et al.*, 1981).

PATIENTS, CONTROLS AND METHODS

Patients

Two hundred unrelated Caucasian patients, indigenous to the Grampian region of Scotland, were studied. All the patients had previously attended the Department of Neurology, Aberdeen Royal Infirmary, and were identified by reviewing accessible notes or computerized data. Patients were selected for study primarily according to their degree of disability over time, the majority having either severe or benign disease, as defined below, and the remainder (21%) intermediate levels of disability. Over 95% of patients contacted agreed to participate in the study. The diagnosis of MS conformed to the clinical criteria of the Poser committee (Poser *et al.*, 1983); 182 patients (91%) were classified as having clinically definite MS, and 18 (9%) as clinically probable. There were 136 females (68%) and 64 males (32%). The mean duration of observation was 16 yrs 9 months (within a maximum of 54 yrs).

Patients were categorized according to disease severity (i.e., benign or severe), clinical course (remittent or progressive), initial symptomatology (optic neuritis, brainstem or predominantly spinal symptoms) and age at onset (first symptoms occurring between 20 and 40 yrs of age or occurring after 40 yrs of age). The following criteria for classification were used.

Benign disease. Patients assigned to this group had a score of 3 or less on the Kurtzke disability scale (Kurtzke, 1961) after 10 yrs from the onset of their initial symptoms. These patients were further subdivided into those with a Kurtzke disability score of 3 or less after 20 yrs disease duration.

Severe disease. Patients assigned to this group had a Kurtzke score of 5 or more within 10 yrs of their first symptom(s). These patients were further subdivided into those with a score of 5 or more within 5 yrs.

Remittent MS. This was defined as a course of disease in which there were distinct attacks with stable phases between relapses. Relapses and remissions were defined by the Poser criteria (Poser *et al.*, 1983).

Progressive MS. This category consisted of patients who showed either progressive evolution of disease from onset or who entered a progressive phase following initial remissions.

Controls

For comparisons, 130 local healthy controls were studied. These, like the patients, were unrelated Caucasians indigenous to the region. Approximately 90% were hospital personnel at the Aberdeen Royal Infirmary and the remainder were blood donors. In view of the high prevalence of MS in the region, subjects with a positive family history of MS or any previous neurological symptoms were excluded from the control group.

HLA Typing

Lymphocytes were separated from 20 ml of heparinized peripheral blood by the standard technique of Ficoll/hypaque density gradient centrifugation (Böyum, 1968). The cells were then frozen in a mixture of 75% fetal calf serum, 8% dimethylsulphoxide in culture medium at a final concentration of 5×10^6 cells/ml in liquid nitrogen (Cryoson biological freezer).

When required for tissue-typing the stored lymphocytes were thawed rapidly in a 37° C water bath and resuspended in 2 ml of McCoys 5A medium for separation into T and B cells by means of a modification of the Mann technique (Mann *et al.*, 1975), using goat antihuman $F(ab')^2$ coated 60 mm petri dishes (Falcon). The lymphocyte suspension was added to the coated dishes and incubated at 37° C for 30 min.

Following incubation the medium was gently agitated and nonadherent (T) lymphocytes aspirated. Adherent (B) lymphocytes were detached through the addition of 'competition reagent', PBS containing 0.5% EDTA and 10% AB serum, and further incubation at 37° C for 30 min.

The T-lymphocyte suspension (2×10^6 cells/ml) was used to type antigens of the HLA-A, -B and -Cw series; the B lymphocyte suspension was typed for HLA-DR and DQw antigens. T- and B-enriched cell suspensions from the same peripheral blood sample were always tested in parallel in lymphocytotoxicity tests on 60 well microtest plates (Falcon). 0.2% nigrosin was used to assay cell death and the plates were read, within an hour of incubation, to estimate the percentage of cell lysis. If cell death was greater than 20% above background cell debris it was judged positive. Tests that were technically unsatisfactory were repeated as required.

The typing sera used to define the Class I and II antigens were obtained locally or donated by typing laboratories. All had either been used in the Histocompatability Workshops or characterized by testing on cell panels previously tested with Workshop sera. In most instances at least 4 well-defined antisera were used for detection of each HLA specificity and positive typing for any antigen was based on concordant reactions with at least two. At the earlier stages of the study we lacked reliable reagents for DQw2 and DQw3, and we are therefore only able to include data on DQw1 which has been consistently well defined.

Complement Allotypes

Serum and plasma samples from patients and controls were stored at −70° C until required. Bf allotyping was carried out by high voltage agarose electrophoresis of serum samples in 0.8% weight/volume agarose (Sigma type II) using a barbital-calcium lactate buffer, pH 8.6, followed by immunofixation according to the method of Alper *et al.* (1972). C4 allotyping was performed on edetic acid plasma, treated overnight with neuraminidase from *Clostridium perfringens* (Sigma type

VIII). Electrophoresis was performed on the desialized samples in 0.6% agarose (Seakem ME) in tris-glycine-barbital buffer, pH 8.2, according to the method of O'Neill *et al.* (1978). Immunofixation of the C4 bands was achieved using rabbit antihuman C4 complement (Atlantic antibodies). Functional detection was performed using an overlay method similar to that described by Lachmann and Hobart (1978*a*). Heterozygotes and half-nulls were detected by a significant decrease in the intensity of staining at either locus.

C2 typing was performed by isoelectric focusing sera in 5% polyacrylamide gels essentially as reported previously (Lachmann and Hobart, 1978*b*, Glass *et al.*, 1976). The gels were washed using the technique described by Meo *et al.* (1976) and the bands visualized with a functional overlay similar to that used for C4 but substituting 2% normal heat-inactivated human serum for C4 deficient guinea pig serum.

Statistics

The probability value (P) for each statistic was computed for significance using the χ^2 test. Yates correction for continuity was applied. Correction was made for the number of antigens tested if this was high or when warranted by the size of the patient subgroups.

RESULTS

Total population

Class I and II antigens. Out of 200 patients with MS and 130 controls, 194 and 128, respectively, were successfully tissue-typed for Class I antigens and 178 and 128, respectively, were tissue-typed for the Class II DR antigens. Failure to obtain a satisfactory tissue-type resulted from either the collection of insufficient blood at venesection or poor cell viability following thawing from storage.

The results for Class I typing show higher frequencies of HLA-A3 and HLA-B7 in the patient group than in the controls (37.1% and 43.3%, respectively, in patients versus 27.3% and 38.3% in controls), but in neither case are the differences statistically significant. It is important to note that the frequencies of these antigens in our patient group are similar to those found in comparable studies on Caucasian patients with MS in which a significant association has been shown; however, the frequencies of these antigens in our control population are significantly higher than those found in other normal European Caucasian populations. HLA-B7, for example, was present in 38.3% of our local control group, compared with a figure of 17.3% for the group of European Caucasians documented at the 8th Histocompatibility Workshop ($P<0.001$) (Terasaki, 1980). HLA-A2 was under-represented in our patient group (39.2% versus 58.6%, $\chi^2 = 10.9$, $P<0.001$).

Results for DR Typing (Table 1) show a similar trend for DR2. This antigen was present in nearly half of the patients (49.4%), a figure comparable to that noted in other Northern European MS populations. However, the local control group also had a high frequency of DR2 (40.6%) only slightly lower than our patient group; the difference was not statistically significant. DR2 was also significantly raised in local controls when compared to the 8th Workshop panel of normal European Caucasians ($P < 0{\cdot}001$). In the Grampian population HLA-DRw6 was increased in MS compared with controls ($P<0.03$); DR1 was also

TABLE 1. ANTIGEN FREQUENCIES OF HLA-DR AND DQW1

	MS $n = 178$ (%)	*Controls* $n = 128$ (%)	χ^2	*P value*	*P corrected for number of antigens*
HLA-DR1	13.5	9.4	0.8	n.s.	n.s.
DR2	49.4	40.6	2.0	n.s.	n.s.
DR3	32.0	28.9	0.2	n.s.	n.s.
DR4	16.8	30.5	7.1	< 0.01	n.s.
DR5	6.2	14.1	4.5	< 0.05	n.s.
DRw6	21.3	10.9	5.0	< 0.03	n.s.
DR7	21.9	31.2	2.4	n.s.	n.s.
DRw8	0.6	0.0	—	—	—
DRw9	2.2	2.3	—	—	—
DRw10	0.0	—	—	—	—
DQw1	77.5	62.5	7.6	< 0.006	< 0.018

raised but not significantly. HLA-DR4 and DR5 were significantly decreased ($P<0.01$ and $P<0.05$). These differences were not significant when corrected for the number of antigens tested.

It is interesting that the recently defined antigen HLA-DQwl shows cross-reaction with DR1, DR2 and DRw6. When the patient and control groups were tested with antisera detecting DQw1, 77% of patients were positive compared with 62% of controls, ($\chi^2 = 7.6$, $P<0.006$). This raises the possibility of a significant association between HLA-DQwl and MS.

The frequencies of selected antigen phenotype combinations were also studied. Although the combinations A3-B7, B7-DR2 and A3-B7-DR2 were increased in MS (22.2%, 31.5% and 15.7%, respectively) they did not differ significantly from the corresponding control frequencies (16.4%, 24.2% and 10.9%). The combinations of A1-B8, B8-DR3 and A1-B8-DR3 had similar frequencies in patients (24.7%, 19.7% and 17.4%) and controls (20.3%, 22.6% and 17.2%). DR2 and DR3 were found together in 21 of 178 MS patients (11.8%) and 12 of 128 (9.4%) controls (n.s).

HLA-B12, its subtype B44, and DR7, were under-represented in our patient group as individual antigens, and the combined frequency of the phenotypes B12-DR7 and B44-DR7 was lower in the MS group (24.2%) than in controls (32.3%) although the difference was not statistically significant. These phenotypes, however, were significantly under-represented in patients also carrying MS-associated antigens (either B7 or DR2) compared to controls ($\chi^2 = 8.7$, $P<0.01$). This supports the suggestion that these phenotypes may contain a protective genetic factor (*see* Discussion).

Class III antigens. Complement Factor B (Bf). The phenotype frequencies of Bf in 200 MS patients and 128 controls are shown in Table 2. No significant deviation of phenotype distribution was noted between the two groups. The association of the two commonest Bf phenotypes (BfS and BfF) with individual DR antigens was

TABLE 2. PHENOTYPE FREQUENCIES OF FACTOR B, C4A AND C4B ALLELES

	MS n = 200 (%)	*Controls* n = 128 (%)
Factor B (Bf)		
SS	62.5	60.2
SF	27.5	32.0
FF	4.5	5.5
FF1	0.5	0.0
All F phenotypes*	34.0	38.3
SF1	1.5	0.8
SS1	3.5	1.6
S1S1	0.0	0.0
F1F1		
S1F1		
Complement C4		
C4 AQ0	31.5	29.5
A2	7.5	4.5
A3	88.0	80.5
A4	17.5	15.5
A5	0.0	1.0
A6	5.0	11.5
C4 BQ0	14.5	14.0
B1	95.0	89.0
B2	19.5	17.0
B3	5.5	4.5
B4	0.5	0.0
B5	0.0	1.5

* Includes SF and FF1 heterozygotes and FF homozygotes. χ^2: no significant differences.

analysed. In no instance was there any significant differences between the pair-wise frequencies in the patient and control groups. It is possible that Bf phenotypes may be a contributing factor to susceptibility to MS; however, our data provided no evidence in support of this hypothesis.

Complement C4A and C4B. No significant differences between patient and control groups were found (Table 2). One interesting finding was that the frequency of C4A and C4B null alleles together total 46% in the patients with MS and 44% in the control population, figures which are higher than in other Caucasian populations (Alper *et al.*, 1984). Furthermore, it is likely that the frequency of null alleles has been somewhat underestimated because if one is present at both C4A and C4B it may be undetectable without family studies. Nevertheless errors of assignment are likely to be similar in the patient and control groups. This situation is consistent with the other differences seen in the Class I and II antigen frequencies in this population as a whole.

Complement C2. The patient and control groups were very similar with respect to the C2 polymorphisms detected by isoelectric focusing. All 200 patients and the 128 control subjects tested carried the C2*C phenotype. Seven patients (3.5%) also carried the phenotype C2*B but none of the control group expressed this allele.

Results in Subgroups of Patients with MS

Disease severity. Sixty-eight patients could be classified as having severe disease and in 50, significant disability had occurred within 5 yrs (Kurtzke disability score >5.0). Ninety patients had benign disease and 48 of these had only minimal disability after 20 yrs disease duration (Kurtzke disability score <3.0).

Class I and II antigens. Considering the MS-associated antigens first, the overall group of patients with benign MS (90 individuals) were characterized by increased frequencies of HLA-B7, DR2 and B7-DR2 (47.1%, 55.5% and 33.3%, respectively, vs 38.8%, 40.6% and 24.4% for the controls) and a decreased frequency of HLA-A2 (40.2% vs 58.6%); of these only the differences for A2 and DR2 attained statistical significance with uncorrected P values. In severe disease HLA-B7, DR2 and B7-DR2 showed similar frequencies when compared with the control population.

HLA-A1, B8 and A1-B8 showed increased frequencies in patients with severe disease overall (68 individuals; 46.9%, 31.2% and 26.6%, respectively, vs 34.4%, 27.3% and 20.3% in controls), whereas the antigen combinations involving DR3 (i.e., B8-DR3, A1-B8-DR3 and DR2-DR3) were similar to the control frequencies.

None of the above differences was statistically significant when corrected for the number of antigens tested even when the more extreme severe and benign groups were compared.

HLA-DRw6 was significantly increased and HLA-DR4 significantly decreased in the severe group as a whole, and the differences for these antigens became highly significant when the most severely affected patients (Kurtzke disability score >5.0 within 5 yrs) were considered ($P^{\text{uncorr}} < 0.005$ and $P^{\text{uncorr}} < 0.01$, respectively; Table 3). Only the increase in HLA-DRw6 remained significant after correcting for first order error ($P^{\text{corr}} < 0.05$). In patients with benign disease differences in DRw6 and DR4 were not seen.

HLA-DQw1 was increased equally in both polar groups (i.e., the most severe and the most benign patients) when compared with controls ($P < 0.05$).

Class III antigens. Factor B, Complement C4 and C2 allotypes showed no deviation from control frequencies in either severe or benign disease and no significant difference was observed between the two clinical subgroups.

Clinical course. One hundred and fifty-two patients were classified as having remittent disease and 48 patients 'progressive' MS; 136 and 42 patients, respectively, were successfully DR typed. In patients with remittent disease, HLA-DR2 and HLA-DQw1 were significantly more frequent than in the group of patients with nonremitting disease or the control population (Table 3).

TABLE 3. HLA TYPING ACCORDING TO DISEASE SEVERITY AND CLINICAL COURSE

	Severe (*A*)† $n = 46$ (%)	*Benign* (*B*)‡ $n = 44$ (%)	*Controls* (*C*) $n = 128$ (%)	*Differences between groups*		
				AvB	*AvC*	*BvC*
DR1	22	4	9	4.4*	n.s.	n.s.
DR2	43	54	41	n.s.	n.s.	n.s.
DR3	28	29	29	n.s.	n.s.	n.s.
DR4	9	27	31	4.1*	7.5**	n.s.
DR5	6	11	14	n.s.	n.s.	n.s.
DRw6	30	23	11	n.s.	8.1***	n.s.
DR7	24	16	31	n.s.	n.s.	n.s.
DRw9	4	2	2	n.s.	n.s.	n.s.
DQw1	78	80	62	n.s.	3.8*	4.3*
DR2-DR3	9	14	9	n.s.	n.s.	n.s.
	Remittent (*A*) $n = 136$ (%)	*Progressive* (*B*) $n = 42$ (%)	*Controls* (*C*) $n = 128$ (%)	*Differences between groups*		
				AvB	*AvC*	*BvC*
DR1	13	14	9	n.s.	n.s.	n.s.
DR2	54	33	41	4.9*	4.5*	n.s.
DR3	37	17	29	5.1*	n.s.	n.s.
DR4	180	12	31	n.s.	4.6	4.8*
DR5	4	12	14	n.s.	5.9*	n.s.
DRw6	20	26	11	n.s.	n.s.	4.7*
DR7	18	36	31	5.1*	5.9*	n.s.
DRw9	2	5	2	n.s.	n.s.	n.s.
DQw1	79	71	62	n.s.	8.6***	n.s.
DR2-DR3	15	2	9	4.7*	n.s.	n.s.

† Kurtzke disability score > 5 within 5 yrs. ‡ Kurtzke disability score < 3 after 20 yrs. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.005$. Only *** remained significant when corrected for number of antigens.

In progressive MS, significant findings were that HLA-DRw6 was over represented and DR4 under-represented when compared with controls ($P<0.05$) as noted for severe disease, and DR2 and DR3 under-represented when compared with remittent disease ($P<0.05$). With the exception of HLA-DQwl in remittent disease, in each case statistical significance was lost when multiplied by the number of antigens tested.

Age of onset. Of 200 MS patients: 12% (24/200) developed symptoms before the age of 20 yrs, 62.5% (125/200) between 20 and 40 yrs of age and 25.5% (51/200) over the age of 40 yrs. Remittent and benign disease predominated in patients below the age of 40 yrs at onset and a significantly higher proportion of patients over 40 yrs at onset had severe or progressive MS ($P<0.005$; Table 4).

Although there were observed differences in the frequencies of several DR antigens between the subgroups of patients classified according to clinical course, when classified on the basis of age at onset of MS, no significant differences were seen.

TABLE 4. CLINICAL CHARACTERISTICS ACCORDING TO AGE AT ONSET

	10–40 yrs *n = 149* (%)	*Over 40 yrs* *n = 51* (%)	
Disease severity			
Severe	25	59	$\chi^2 = 13.9$
Benign	49	27	$P < 0.005$
Unclassified	26	14	
Disease course			
Remittent	80	57	$\chi^2 = 9.3$
Progressive	20	43	$P < 0.005$

Age at onset was also not influenced by the distribution of Class I or Class III antigens.

Initial symptomatology. In 38 patients (19%) optic neuritis was the first manifestation of MS and the mean age of onset was 30.3 yrs; 61 patients (30.5%) presented with predominantly brainstem symptoms, and the mean age was 32.7 yrs; 99 patients (49.5%) had symptoms attributable to plaques in the spinal cord, and the mean age of onset in this group was 35.3 yrs. Two patients could not be classified because the mode of onset of their disease was less certain.

A total of 24% of patients presenting with optic neuritis, 36% of patients with brainstem symptoms and 38% of those of presumed spinal origin subsequently developed severe disease. The corresponding figures for those who developed benign disease were 55, 42 and 40%, respectively. Patients with optic neuritis as a first symptom were therefore more likely to follow a benign course but this could not be predicted from their HLA profile.

DISCUSSION

Our most striking findings were that although the frequency of HLA-DR2 in patients with MS in the Grampian region (49.4%) was comparable to that reported in other European studies on MS, a high frequency of HLA-DR2 was also observed in normal subjects from this region (40.6%). The difference in frequencies of DR2 between the two groups was not significant. Our observations in the Grampian region are similar to those of Poskanzer *et al.* (1980*b*) in the Orkney Islands and are in accord with Compston's (1981) suggestion that MS is particularly prevalent where the frequency of DR2 in the population is high, the failure to observe a significant difference between patient and control groups being due to the high frequency in the latter. A similar suggestion in relation to B7, which is high in the normal Grampian population, had been made by Shepherd and Downie (1978).

The second interesting finding was the significant over-representation of HLA-DQw1 in patients with MS ($P < 0.006$) when compared with the local population. As might be expected because of the well-established linkage disequilibria between

HLA-DQw1 and HLA-DR1, 2, and w6 (Albert *et al.*, 1984), frequencies of the latter 3 HLA-DR antigens were all higher in our patient group than in the sample of normal subjects.

The suggestion that susceptibility to MS is determined by a single gene in linkage disequilibrium with DR2, rather than DR2 itself, has been made by a number of workers (Terasaki and Mickey, 1976; Stewart *et al.*, 1981) because of the incomplete correlation between the presence of DR2 and all cases of MS, particularly in patients with different ethnic origins. The DQ locus is known to show strong linkage disequilibrium with the DR locus and therefore deserves investigation as a disease marker for MS. Our data suggest that DQw1 is more closely correlated with MS than DR2 or any allele of the DR series in the Grampian population.

In earlier studies made before the DR series had been defined at the 7th Histocompatibility Workshop (Bodmer *et al.*, 1978), the locally defined B lymphocyte alloantigen, BT101, was found in 83% of a group of 59 Caucasian patients with MS attending the National Hospital in London; the frequency of BT101 in 30 normal individuals was 33% and this difference was significant ($P < 0.003$; Compston *et al.*, 1976). In that study BT101 was found to be largely equivalent to DR2, although the two sera used to define it showed some cross-reaction with DR1 positive and DRw6 positive individuals. We have compared the original sera 'BEW' and 'SEW' used to define BT101 (Compston *et al.*, 1976) with a pool of 5 more recent sera defining DQw1. There was a clear correspondence (unpublished data). It thus seems from our two studies in different regions of Great Britain that DQw1 is more closely associated with MS in British patients than DR2. This suggestion is supported by the preliminary studies with HLA-DQβ gene probes (Cohen *et al.*, 1984) which indicate an abnormal distribution of DQ alleles in French patients with MS.

Another possible explanation for the lack of complete correlation between the presence of an HLA-D region antigen and MS is that the disease is clinically heterogeneous. We have approached this problem by analysing groups of patients who have been shown by follow-up to have different clinical courses. We had confidence in the patient classification because of the special circumstances of the neurological service in the Grampian region as outlined earlier. When patients were divided into two groups with contrasting clinical courses, benign and severe, some interesting differences were observed.

HLA-DQw1 was increased with equal frequency in both the severe and benign subgroups when compared with controls. Although DR1 and DRw6 were at their highest frequencies in the subgroup of 46 patients with the most severe form of the disease, the frequency of DR2 in this group was almost identical to that found in the control population. HLA-DR3 has been reported previously as a marker for disease severity (de Moerloose *et al.*, 1979; Madigand *et al.*, 1982). In our material the frequency of DR3 did not differ significantly between the benign and severe disease subgroups. Overall it would seem that HLA antigens do not appear to influence disease severity.

Another way of classifying the patients clinically is according to whether the disease follows a remittent or progressive course. In our study, DR2 and DR3 was significantly associated with a remittent rather than progressive course. Experience contrary to that reported here has been described by Jersild *et al.* (1973) and more recently by Stendahl-Brodin *et al.* (1979) and Raun *et al.* (1980). These workers reported an increased frequency of HLA-Dw2 in patients with severe and progressive disease. However, the number of patients in the first two studies was small and there was a bias in favour of severe disease in the third. The studies of Collins *et al.* (1978) and Madigand *et al.* (1982) using more clearly defined clinical subgroups of larger size found no correlation between HLA-DR2 and severe or progressive disease.

An increased representation of B8-DR3 phenotypes has also been noted in several HLA studies in MS (de Moerloose *et al.*, 1979; Madigand *et al.*, 1982) raising the suggestion that an allele associated with this combination augments susceptibility to MS. In addition, Madigand *et al.* (1982) postulated the presence of another allele associated with the haplotype B12-DR7 which exerts a protective influence against MS and is most effective in the absence of the 'MS associated' alleles B7 and DR2. We obtained similar results in our study but the associations were weaker raising doubt as to their original significance.

Limited attention has been paid in the study of MS to the frequencies of the polymorphic variants of the HLA-linked complement loci—Factor B (Bf), C2, C4A, and C4B. Stewart *et al.* (1979) observed an increased frequency of BfS in MS patients but attributed their results to linkage disequilibrium between HLA-DR2 and BfS. In the present study there were no significant differences between patients and normal subjects with respect to the Bf alleles. The unusually high frequency of DR2 in normal subjects of the Grampian region may account for the similar frequencies of BfS alleles found in the respective groups. A previous study by Fielder *et al.* (1981), in the south-east of England, had shown a low frequency of BfF in patients with clinically definite MS but not in patients with isolated optic neuritis. Because it is known from previous follow-up studies that 60–80% of patients with isolated optic neuritis ultimately develop MS (Compston *et al.*, 1978), Fielder *et al.* (1981) suggested that the BfF allele was a marker for progression of the disease. The present study does not support this idea since there was no significant difference in frequency of Bf alleles between normal subjects and patients with MS even when the patients were divided clinically into those with severe or benign disease. Our present results are in agreement with those of Bertrams *et al.* (1981) for a West German population.

All patients and normal subjects were also typed for the polymorphisms of C2, C4A and C4B. There were no significant differences in phenotype frequencies of the C4A and C4B alleles between the two groups. In a family study of 13 sib-pairs suffering from MS an over-representation of C4A4 and B2 was found by Schröder *et al.* (1983). Our data do not indicate any substantial increase of these polymorphisms either in the entire group of patients or the clinical subgroups. The combined frequency of null alleles of C4A and C4B in the normal Grampian population is somewhat higher than that noted for a North American Caucasian population (Alper *et al.*, 1984) but this difference may have occurred as the result of ethnic variation.

C2*C defined by immunofixation after isoelectric focusing has now been split into subtypes by restriction enzyme analysis (R. R. Campbell and R. D. Porter, personal communication). It remains possible that although an overt association between C2 polymorphisms and MS was not detected in this study, an association may come to light if the newer, more refined methods are used.

The group of patients studied have shown the usual pattern of clinical features, with the majority of cases, particularly in the younger age group, following a remitting and relapsing course. No striking HLA associations with the age of onset, or initial clinical features were found.

From previous studies, it is evident that susceptibility to MS is partially governed by an HLA region gene, or genes, showing a close association with HLA-DR2. However, because of the incompleteness of the association, for which this study provides further evidence, it is widely believed that DR2 is not itself a single susceptibility gene. We have shown here a significant association between MS and DQw1 in a population in which there is no apparent association between MS and DR2. There is evidence for a similar association in southern England, and French studies using restriction enzymes also indicate a disturbance of DQw antigen frequencies in MS. It will now be important to determine whether the association is found in other populations with (e.g., North American and Australian Caucasians) and without (e.g., Japanese) an association between MS and DR2. Whether additional genetic factors are involved remains an open question although we have found no evidence for the hypothesis that polymorphism of one of the HLA region complement genes strongly influences susceptibility. Certain Gm allotypes have been reported to occur with increased frequency in MS (Pandey *et al.*, 1981; Propert *et al.*, 1982) and we are at present investigating the distribution of Gm allotypes in the same Grampian populations.

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IDIOPATHIC CRANIAL POLYNEUROPATHY

A FIFTEEN-YEAR EXPERIENCE

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SUMMARY

Fourteen cases of idiopathic multiple cranial neuropathy seen over fifteen years are reviewed and contrasted with 6 cases of the Tolosa-Hunt syndrome, the closest and better known clinical entity. The syndrome consists of subacute onset of facial pain preceding the onset of cranial nerve palsies. There were 5 men and 9 women aged 21 to 83 years. Eight of the 9 patients treated with corticosteroids showed improvement, with pain usually receding within 48 hours. The cerebrospinal fluid was abnormal in 7 of 12 cases, with either a mild pleocytosis or raised protein content. The cranial nerves most frequently involved were the third and sixth. Motor nerves were affected more than sensory. Corticosteroid therapy appeared to hasten recovery of function. Clinical features are shared by both syndromes, the resulting spectrum of illness probably reflecting diverse aetiologies. Historical perspectives, differential diagnosis and aetiological considerations are discussed so that a coherent prospective clinical approach to the problem can be developed.

INTRODUCTION

The syndrome of multiple cranial neuropathy is periodically encountered in neurological practice. Typically patients present with facial pain, involvement of mostly motor cranial nerves and often improve with corticosteroid treatment. Many of the reported cases have been from Asia (Kreindler and Macovei-Patrichi, 1968; Ratnavale, 1968; Steele and Vasuvat, 1970; Takahashi, 1974; Hokkanen *et al.*, 1978). In addition, some patients have been reported with painless multiple cranial neuropathy who were presumed to have an oligosymptomatic form of the Guillain-Barré syndrome (Munsat and Barnes, 1965). Isolated cranial nerve palsies have also been reported as a consequence of both mycoplasma infection and infectious mononucleosis (Schnell *et al.*, 1966; Murray *et al.*, 1975). Most cases of painful cranial nerve palsies involving the oculomotor nerves have been designated the Tolosa-Hunt syndrome (Tolosa, 1954; Hunt *et al.*, 1961; Hunt, 1976; Kline, 1982). To characterize further the clinical features and natural history of multiple cranial neuropathies we reviewed all cases presenting in a span of fifteen years at the Massachusetts General Hospital and compared them with 6 cases of Tolosa-Hunt syndrome seen in the same period.

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METHODS

A computerized search was made of all cases carrying diagnoses of cranial nerve palsy, multiple cranial nerve palsies, Tolosa-Hunt syndrome, mycoplasma, infectious mononucleosis, listeria, syphilis, carcinomatous meningitis and herpes zoster. Cases with involvement of a single cranial nerve, congenital cases and those associated with trauma, neuromuscular, demyelinating and cerebrovascular disease were excluded. Over 4,000 cases were initially listed. Of these, approximately 500 charts were selected for scrutiny based on brief computerized clinical descriptions. Eleven cases of idiopathic cranial neuropathy (plus 3 personal cases), including 1 associated with mycoplasma infection, and 6 probable Tolosa-Hunt cases were identified. Criteria for diagnosis of multiple cranial neuropathy were: involvement of at least two cranial nerves, unilateral steady facial pain, symptoms lasting days or weeks, spontaneous remission and recurrences and absence of involvement of other parts of the nervous system. All 6 cases of the Tolosa-Hunt syndrome met the criteria of Hunt for this syndrome (Hunt, 1976). Four of these cases had typical cavernous sinus venograms, and follow-up for two or more years in all cases revealed no other diagnosis. In every case, all relevant diagnostic tests performed are reported.

RESULTS

There were 5 men and 9 women with multiple cranial neuropathy aged 21 to 83 years (Tables 1–3). The Tolosa-Hunt cases are shown in Tables 4–6; there were 4 men and 2 women aged 33 to 67 years.

Headache and Facial Pain

In cases of multiple cranial neuropathy, pain was present in 12 of 14 and anteceded the neuropathy by a few hours to three and a half months. In Case 6, pain commenced several days after the nerve palsies. The pain was aching, deep, constant and unrelenting, but never throbbing or with photopsias. Nausea and vomiting were present only in Case 8. The pain was localized to the temple or frontal area in 9 patients and it radiated into the orbit in 8. In individual cases pain was localized to the cheek, the earlobe, the lateral neck, nose and scalp.

In the Tolosa-Hunt cases, pain preceded onset of cranial nerve signs by three days to one year. Pain was restricted to the orbit in 5 of the 6 cases and was also felt in the frontal, temporal or vertex regions in 4 cases. The pain was constant except in 1 patient with sharp bursts of pain in the left inner canthus for minutes or hours. Photopsia, scotomas and nausea or vomiting were lacking.

Corticosteroid response. Six patients with pain associated with multiple cranial neuropathy received prednisone (20–60 mg/d). Five had complete pain relief in 12 h to a few days; 1 had no response. In untreated patients the pain resolved in seven days to twelve weeks and typically lasted four to eight weeks. All 3 patients with Tolosa-Hunt syndrome who received corticosteroids were free of pain in less than 24 h. In untreated patients pain lasted three days to twenty weeks.

Cranial Nerves

The nerves most frequently involved were VI (12/14), III (6/14), V (5/14), IV (3/14) and VII (4/14). The lower nerves VIII, IX and X were involved in 3 cases, and

XI and XII in 2 cases. Cases 6 and 10 had a transient decrease in vision that resolved. Anisocoria with unequally reactive pupils was present in 3/14 cases and 1 additional case had a transient fixed dilated pupil. Ptosis was prominent in 3/14 cases and Case 8 was thought to have mild proptosis. Conjunctivitis was present in 2. Periorbital oedema was not present. Taste was diminished in Case 8. Involvement of cranial nerve VIII was manifested by decreased hearing in Case 1, sustained nystagmus in Case 11 and tinnitus in Case 14.

TABLE 1. MULTIPLE CRANIAL NEUROPATHIES OF UNCLEAR AETIOLOGY. FACIAL OR CRANIAL PAIN

Case	*Age*	*Sex*	*Duration before CN palsies*	*Patient's description*	*Distribution*	*Total duration*	*'Steroid response'*
1	76	M	Over 10 days	'Severe, deep aching'	L ear, orbit, forehead	2 wks	12 h
2	73	F		None	—	—	NA
3	60	F	1 day, sudden	'Headache'	L temporal	1 wk	NA
4	23	F	8 wks	'Throbbing'	R fronto-temporal, retro-orbital	9 wks	NA
5	68	F	12 days	'Steady ache'	R lat neck, fronto-temporal	1 wk	NA
6	67	M	Followed CN palsies	'Mild'	R orbital	'Days'	Yes, days
7	38	M	—	None	—	—	NA
8	26	F	3 wks	'Headache, nausea, vomiting'	L frontal	4 wks	NA
9	83	F	2 days	'Headache'	Bitemporal, vertex	8-12 wks	NA
10	62	M	14 wks	'Painful'	R eye	16 wks	Yes, days
11	49	F	4 wks	'Sharp, shooting'	L, then R-sided radiating to orbit	8 wks	No response
12	21	M	10 wks	'Severe headache'	Vertex, orbits, nose	10 wks	Yes, days
13	42	F	12 wks	'Painful numbness'	Retro-orbital and over R brow, L face	12 wks	Yes, days
14	53	F	2 wks	'Increasingly severe'	Retro and periorbital	8 wks	NA

NA = not applicable CN = cranial nerve

In the Tolosa-Hunt syndrome, cranial nerve II was involved in 2 patients, III in 6, IV in 1, V in 4, VI and VII in 3. In 1 patient the facial nerve was involved on alternate sides with recurrence. Involvement of the optic nerve consisted of a left superior quadrantanopia and subjective decrease in visual acuity in another case. All patients had ptosis and 3 of the 6, anisocoria with unequally reactive pupils. Eyelid oedema was noted in Case 5, and Cases 1 and 4 had mild proptosis.

Corticosteroid response. Nine of the 14 patients with idiopathic cranial neuropathy (with or without pain) were treated with steroids. Three noted significant improvement in neuropathy in 24–48 h, 4 in 'days', and 1 over four weeks (Case 14).

TABLE 2 MULTIPLE CRANIAL NEUROPATHIES OF UNCLEAR AETIOLOGY· CRANIAL NERVE INVOLVEMENT

Case	Onset of deficit over	Side	*Cranial nerve*											Duration of CN deficit	Residual deficit	'Steroid response'	Recurrence	Follow-up (yrs)
			II	III	IV	V	VI	VII	VIII	IX	X	XI	XII					
1	5 days	L				×	×	×	×	×	×			4 wks	None	Yes, 1 day	N	3½
2	4 wks	R								×	×	×		8 wks	None	Yes,* 1 day	N	5
		L										×						
3	'Sudden'	L		×	×		×							?	No improvement after 1 wk	NA	?	Lost to F/U
4	2 wks	R		×	×	×(V₁)								> 3 wks	No improvement after 3 wks (second episode)	NA	Y	4 (since 1st episode)
5	12 days	R					×	×						4 wks	None	NA	N	1
6	6-8 wks	R	×	×	×		×							4 wks	None	Yes, days	N	7
7	'Sudden'	R					×	×						12 wks	None	Yes, 2 days	N	3 mo
8	3-4 days	L		×	×	×(V₁)		×						2 wks	None	NA	?	Lost to F/U
9	On awakening	L		×	×		×							16 wks	None	NA	N	†
10	8 wks	R	×			×(V₁)	×							12 wks	None	Yes, days	N	20
11	6 wks	R					×		×	×	×	×	×	9 yrs	Swallowing, abn. taste	None	N	9
12	Over 1 day	R		×			×							16 wks	None	Yes, days	Y, 2 yrs	5
		L					×											
13	'Gradual'	R					×							< 3 wks	—	Yes, days	Y, 8 wks, 20 wks	Lost to F/U
		L				×(V₂, V₃)												
14	Over 1 wk	R						×						20 wks	None	Yes, 4 wks	Y, 20 wks	9 mo
		L							×				×					

* Increasing dysphagia each time steroids were tapered. † Patient died from unrelated causes 2 yrs after the polyneuropathy. Examination of intracranial contents was negative Y = yes N = no F/U = follow-up

TABLE 3 MULTIPLE CRANIAL NEUROPATHIES OF UNCLEAR AETIOLOGY INVESTIGATIONS

	CSF						*Radiology*		
Case	Protein (g/l)	Cells (mm³)	ESR (mm/hr)	Serol	ANA	WBC	CT	Angiography	Skull x-ray
1	0 38	8L	15	Neg	Neg	Nl	Neg	—	Neg
2	0 70	2L	21	Neg	—	Nl	—	—	—
3	—	—	10	—	—	—	—	Nl, left side	Neg.
4	0 42	0	—	—	—	—	—	Nl	Neg
5	0 55	34M	10	Neg	Neg	Nl	—	—	Neg
6	0	0	—	—	—	Nl	Neg	†	—
7	0.48	0	6	—	—	—	Neg	—	*
8	0 25	0	—	Neg	—	—	—	—	Neg
9	0 75	0	—	Neg	Neg	Nl	—	Nl	*
10	0 40	0	15	—	—	—	—	Nl	Neg
11	0 50	2L	—	Neg	—	—	—	Nl	Neg ‡
12	0 37	0	9	—	Neg	—	—	—	Neg
13	0 33	4L	60	—	Neg	Nl	Neg	—	Neg.
14	0 33	2L	—	—	—	Nl	Neg with metrizamide	—	Neg

* Slightly enlarged sella without erosion † Right carotid stenosis and increased vascularity in the posterior orbit during venogram ‡ Posterior fossa myelogram was negative, laryngoscopy revealed R vocal cord paralysis Nl = normal ANA = antinuclear antibody tests CT = computed cranial tomography L = lymphocytes M = mononuclear cells

In Case 11 a belated short course of steroids was ineffectual. In the treated patients there was complete resolution of all neurological abnormality by twelve weeks in 7 patients and by sixteen weeks in 1 patient. Case 11 continued to have some dysphagia and abnormal taste nine years later. Steroid therapy was maintained for

TABLE 4. TOLOSA-HUNT CASES: FACIAL OR CRANIAL PAIN

Case	*Age (yrs)*	*Sex*	*Duration before CN palsies*	*Patient's description*	*Distribution*	*Total duration*	*'Steroid response'*
1	33	F	3 wks	'Pain and sinus pressure'	L periorbital	3½ wks	Yes, 24 h
2	67	M	1 wk	'Severe headache'	Bivertex, bitemporal	3 days	NA
3	54	F	3 days after diplopia	'Aching'	R frontal, retro-orbital	3 days	NA
4	54	M	1 wk	'Numb feeling'	R eye, bifrontal	7 days	Yes, 24 h
5	46	M	20 wks	'Paroxysmal, minutes to hours'	R medial canthus	20 wks	NA
6	50	M	1 yr	—	Over and inside R eye	1 yr	Yes, 24 h

TABLE 5. TOLOSA-HUNT CASES: CRANIAL NERVE INVOLVEMENT

			Cranial nerve							*Duration*				
Case	*Onset of deficit*	*Side*	*II*	*III*	*IV*	*V*	*VI*	*VII*	*VIII*	*of CN deficit*	*Residual deficit*	*'Steroid response'*	*Recurrence*	*Follow-up (yrs)*
1	Sudden	R			×			×		36 wks	None	Yes, weeks	Yes, 16 wks	3½
		L		×	×	×(V$_1$)	×	×						
2	Within hours	L		×			×			4 wks	None	NA	None	7
3	Sudden	R	×	×	×	×(V$_1$)	×			4 wks	None	NA	None	1
4	On awakening	R		×		×(V$_1$)	×	×		9 wks	None	Yes, 1 wk	Yes, 3 yrs	3½
5	Gradual onset	L		×		×(V$_2$)				'Several wks'	None	Yes, 5 days	None	7
6	Over 8 wks	R	×	×				×		4 wks	None	Yes, 1 wk	None	2

TABLE 6. TOLOSA-HUNT CASES: INVESTIGATIONS

	CSF						*Radiology*			
Case	*Prot. (g/l)*	*Cells (mm³)*	*ESR (mm/h)*	*Serology*	*ANA*	*WBC*	*CT*	*Angio-graphy*	*Veno-gram*	*Skull x-ray*
1	Nl	0	10	Neg.	Neg.	Slightly ↑	Neg.	Neg.	Pos.	Neg.
2	0.74	5L, 1P	113†	Neg.	—	Nl	Neg.	Neg.	—	Pos.§
3*	0.36	0	3–20	Neg.	—	Nl	Pos.§	Neg.	Pos.	Neg.
4	0.22	0	—	Neg.	—	Nl	Pos.‡	Neg.	Pos.	Neg.
5	0.62	0	2	Neg.	—	Nl	Neg.	Neg.	—	Neg.
6	0.58	6L	25	—	—	Nl	Neg.	Neg.	Pos.	—

* Biopsy of the superior orbital fissure showed dense fibrous tissue. † Temporal artery biopsy was negative for vasculitis. ‡ Slightly enlarged sella, no bony erosion. § The superior orbital fissure was enlarged with local bony erosion noted on tomography. L = lymphocytes. P = polymorph. Nl = normal. ANA = antinuclear antibody tests. CT = computed cranial tomography.

two to three months. There were no reported complications. In 3 untreated patients (Cases 5, 8, and 9), signs cleared spontaneously in two to sixteen weeks. In Case 14, unilateral hypoglossal palsy with lingual atrophy and fasciculations resolved spontaneously over twenty weeks.

Laboratory Tests

None of the patients had symptoms of diabetes mellitus and 8 had a normal fasting blood sugar (FBS) concentration. Two had mildly abnormal glucose tolerance tests. Erythrocyte sedimentation rate (ESR) was normal in 7 cases, while in 1 it was 60 mm/h. Antinuclear antibody tests (ANA) were negative in 4 cases and positive in 1; in that case the LE cell preparation was normal.

In the Tolosa-Hunt cases the ESR was normal in all but 1, in whom it was 113 mm/h with a normal temporal artery biopsy. White blood cell counts and serological tests for syphilis were normal in all patients.

Cerebrospinal Fluid

The cerebrospinal fluid (CSF) was abnormal in 7 of 12 cases with mild protein elevation (0.5–0.75 g/l) or pleocytosis (2–8 lymphocytes/mm^3). Case 5 had 34 mononuclear cells/mm^3. Cultures for bacteria and fungi and cytology (6 cases) were negative. Case 1 had an acute CSF herpes virus titre of 1/128. Case 1 of the idiopathic group and Case 2 with the Tolosa-Hunt syndrome had midzone and early peaks in the colloidal gold curves, respectively. Case 14 had oligoclonal IgG bands in the CSF, while Case 9 had a typical albuminocytologic dissociation. In the

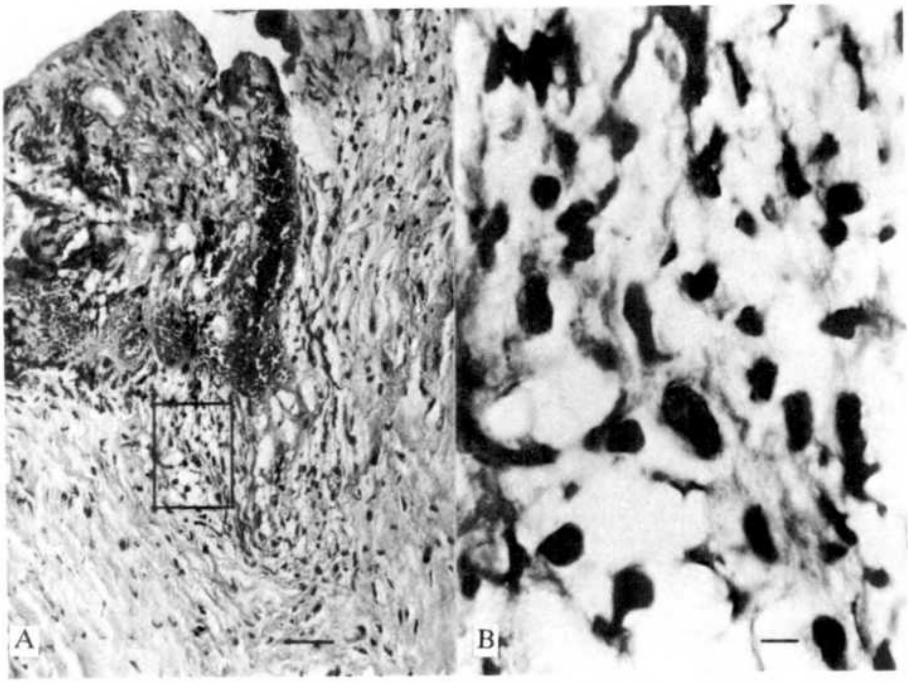

FIG. *Case 3*. Biopsy showing small areas of haemorrhage surrounded by dense fibrous tissue with acute and chronic inflammation. B represents an enlargement of the box in A. (Luxol fast blue, haematoxylin and eosin. A, bar = 250 μm; B, bar = 4 μm.)

Tolosa-Hunt cases, the CSF was normal in 3 cases and there was mild pleocytosis or protein elevation in 3 others.

Neuroradiology

Six patients with idiopathic cranial neuropathy had normal carotid angiograms. Case 6 showed increased vascularity in the posterior orbit during venography. In 4 patients in the Tolosa-Hunt group, venography showed occlusion of the superior orbital vein or poor filling of the cavernous sinus ipsilateral to the symptoms. CT was normal in all, except for 1 case with the Tolosa-Hunt syndrome in which there was asymmetric enhancement of the cavernous sinus.

Pathology

One patient (Case 11) with persistent cranial nerve palsies died ten years after the onset of neuropathy. Necropsy showed focal demyelination limited to cranial nerve IX and the right tractus solitarius. The remainder of the brainstem was normal. Case 3 with the Tolosa-Hunt syndrome had a biopsy of a cystic mass situated just lateral and anterior to the apex of the orbit, in the midportion of the superior orbital fissure. The cyst contained 'yellowish necrotic tissue' (later found to be sterile). Microscopic study of the specimen (fig.) showed 'dense fibrous connective tissue with blood clot and focal acute and chronic inflammation'.

ILLUSTRATIVE CASE REPORTS

Case 1: Multiple Cranial Neuropathy

A 76-year-old man had a sore throat for fifteen days and dysphagia for five days. On admission he had 'severe, deep and aching pain' over the left cheek, ear, orbit and forehead with a left facial palsy. Examination showed a normal body temperature, residual pharyngitis with conjunctivitis and evidence of recent weight loss. There were no skin lesions, lymphadenopathy or organomegaly. The neck was supple. Neurological abnormalities were limited to the left cranial nerves: a partially dilated and sluggishly reactive pupil, lateral rectus palsy, hypaesthesia to touch in the anterior upper border of the pinna, peripheral facial nerve palsy, diminished speech discrimination and poor balance. Taste was diminished on the anterior half of the tongue. Palatal sensation and the pharyngeal reflex were decreased on the left.

The CSF showed 8 lymphocytes/mm^3, a protein content of 0.38 g/l and a midzone colloidal gold curve. Serology, cytology and cultures for bacteria, including M. tuberculosis, and fungi, were negative. The following laboratory tests were normal: full blood count (FBC), ESR, FBS, ANA, latex fixation, serum protein electrophoresis, and syphilitic serology. The tuberculin skin test was negative. A barium swallow was normal. A CT scan, bone scan, and skull x-rays were all normal. The EEG showed minimal left temporal slowing and the brainstem auditory evoked response showed the I-III interwave latency to be at the upper limit of normal. Dexamethasone (4 mg) was given and the pain dissipated in 12 h. He was discharged on a tapering prednisone schedule and three weeks later all symptoms had resolved. There has been no recurrence in four years.

Comment. This case overlaps the syndromes of Tolosa-Hunt, idiopathic Bell's palsy and the multiple cranial neuropathy described by Steele and Vasuvat (1970). Symptoms were preceded by an upper respiratory infection and resolved promptly with steroid therapy.

Case 15: Multiple Cranial Neuropathy Associated with Mycoplasma

A 41-year-old woman awoke from a short sleep with a severe constant generalized headache. Four days after onset, she awoke with horizontal diplopia on right gaze, photophobia, paresthaesiae over the left cheek and mouth, tingling over the left side of the tongue, neck stiffness and a 'funny' appearance of the left eye in the mirror. There was a right lateral rectus palsy with only 2 mm abduction from the midline, a slight decrease in pin prick sensation over the left cheek, a diminished left corneal reflex, and a mild right peripheral facial weakness. The CSF showed a normal pressure, 34 mononuclear white cells/mm^3, glucose and protein concentrations of 3.1 mmol/l and 0.45 g/l, respectively, a negative VDRL test and negative culture. A CT scan was normal. Laboratory tests including FBC, ESR, heterophile antibodies, ANA, rheumatoid factor, hepatitis antigen, and toxoplasmosis, herpes and cytomegalovirus antibody titres were normal. A tuberculin skin test was negative while that for candida was positive. Incidental hyperparathyroidism was diagnosed. Two days after admission, the CSF showed 93 mononuclear cells/mm^3 but was otherwise unchanged. Within one week the partial left fifth nerve deficit resolved. On the seventh hospital day left facial weakness also appeared and that on the right worsened. Therapy with prednisone (80 mg daily) was started on the twelfth hospital day, with prompt resolution of headache. Facial movement then improved bilaterally but the right sixth nerve palsy was unchanged. Prednisone was maintained for three months. By that time the right sixth nerve weakness had resolved and there was only slight facial weakness. There was complete recovery four months after onset, with no recurrence for two years. When in hospital the mycoplasma complement fixation titre was 1:64. One month after discharge the titre rose to 1:256 suggesting a recent mycoplasma infection.

Comment. This case appears to have been one of multiple cranial neuropathy as a consequence of mycoplasma meningoencephalitis. Several features were atypical from the other cases. The headache was generalized and constant rather than the unilateral throbbing pain encountered in other cases. Also there was a marked CSF pleocytosis of up to 93 mononuclear white cells/mm^3, while no more than 8 white cells/mm^3 were found in the idiopathic cases.

Case 9: Possible Oligosymptomatic Guillain-Barré Syndrome

An 83-year-old woman presented with two days of sharp bitemporal headaches spreading over the vertex. Simultaneously she developed complete ptosis on the left, with diplopia on opening the eyelid. Six days previously she had had 'a mild cold' with rhinitis and sore throat. Past history was otherwise unremarkable.

Examination was notable for fever of 38.3° C due to coincident acute cholecystitis. Mentation was normal. The left pupil was 5 mm in diameter and unreactive, and there was complete left external ophthalmoplegia. There was minimal limitation of lateral movement of the right eye and normal pupillary responses. Both corneal reflexes were sluggish but sensation was otherwise normal. Muscle strength and tone were normal but tendon reflexes could not be obtained at the knees or ankles whereas they had been present at previous examinations.

The initial diagnostic impression was of a nasopharyngeal tumour or intracranial aneurysm. Examination of the CSF showed an albuminocytologic dissociation with a protein content of 0.75 g/l and no cells. Electrodiagnostic studies were not performed. Other studies were unrevealing. Two months later all neurological findings had resolved and knee reflexes had returned. She died with congestive heart failure one year later, and at autopsy no significant neuropathological findings were found.

Comment. This case showed arreflexia with subsequent recovery, involvement of cranial nerves and a CSF albuminocytologic dissociation following an upper respiratory infection. It therefore could be interpreted as an oligosymptomatic form of the Guillain-Barré syndrome. Of note was the presence of sharp headaches at the onset of the cranial nerve palsies similar to most of the idiopathic and Tolosa-Hunt cases. The headaches were bilateral whereas in 5 of the 6 Tolosa-Hunt cases and 11 of the 12 multiple cranial neuropathy cases pain was unilateral.

Case 3: Tolosa-Hunt Syndrome

This 54-year-old woman was in excellent health until eight days before admission, when she experienced the onset of painless diplopia. Five days before admission she developed a continuous aching sensation in the right temple and above the right brow. This became severe by three days before admission and required narcotic analgesics.

Examination on admission was normal except for findings limited to the cranial nerves on the right. Visual acuity was normal but formal testing revealed a superior temporal quadrantanopia. The right pupil was 0.5 mm smaller than that on the left and sluggishly reactive to light. There was mild right ptosis. There was no lateral motion of the right eye, 1 mm of upgaze, 2 mm of medial gaze and 4 mm of downward gaze. The eye did not intort. The corneal reflexes, trigeminal nerve sensation and the remaining cranial nerves were all normal.

Routine laboratory tests were normal. The ESR was 3 mm/h. The CSF showed no cells, protein and glucose concentrations of 0.29 g/l and 3.8 mmol/l, respectively, and negative cultures. Skull x-rays were normal. A CT scan with contrast showed no enhancing lesions but the right orbital fissure was enlarged compared with the left. Tomograms of the right orbital fissure showed smooth widening and erosion of the fissure. An angiogram was normal, as was a bone scan. A cavernous sinus venogram showed obstruction of the right superior ophthalmic vein.

The neuroradiological studies were interpreted as consistent with a small mass involving the right superior orbital fissure. Surgical exploration of this region was therefore undertaken. On removing the orbital bone the surgeon encountered 'a bulging, ballotable cystic mass, just lateral and anterior to the apex of the orbit in the midportion of the superior ophthalmic fissure'. A biopsy was performed on the wall of the cyst and yellowish fluid removed. Pathological examination of the material showed fibrous tissue with chronic and acute inflammation (*see* fig.). Culture of the cyst fluid for fungi, M. tuberculosis and other bacteria was negative. Postoperatively third nerve function improved and repeat visual field testing was now normal. When seen six weeks later the diplopia had resolved and neurological examination was normal. There has been no recurrence in five years.

Comment. This case is of interest since it meets criteria for the Tolosa-Hunt syndrome. The pathological findings of chronic and acute inflammation were identical to those originally described by Tolosa (Tolosa, 1954; Schatz and Farmer, 1972). This case is also of interest in that bony changes were produced by the inflammatory process in the region of the superior orbital fissure. Erosion of the sella turcica has previously been reported with the Tolosa-Hunt syndrome (Polsky *et al.*, 1978). The superior temporal quadrantanopia, which resolved, presumably was due to pressure on the optic nerve.

DISCUSSION

Multiple cranial neuropathy may be a manifestation of several known disorders, yet many cases remain undiagnosed after thorough investigation. We reviewed all cases of multiple cranial neuropathy encountered over fifteen years and compared them with cases of the Tolosa-Hunt syndrome. We found that their shared clinical features encompass a spectrum of illness, probably representing a diversity of clinical and pathological entities, as suggested by some of our cases.

The syndrome of idiopathic, self-limited cranial neuropathies was recognized by Gowers in his textbook as early as 1888. Collier, in 1921, recognized the overlapping spectrum of the superior orbital fissure syndrome with cases of isolated or simultaneous lower cranial neuropathies. He commented on the self-limited nature of the syndrome and its tendency to recur. He referred to 'periostitis or fibrosis' localized to the cranial nerve outlets. Lakke (1962) reported a case of superior orbital fissure syndrome with a cuff of granulation tissue around the carotid artery.

Our cases resembled those previously reported by others (Kreindler and Macovei-Patrichi, 1968; Ratnavale, 1968; Steele and Vasuvat, 1970; Takahashi, 1974; Hokkanen *et al.*, 1978). The patients presented with unilateral constant aching pain, typically retro-orbital, and usually preceding neurological symptoms by several days. The pain often required narcotic analgesia but was infrequently associated with nausea and vomiting. Cranial nerve palsies developed suddenly. The nerves most commonly involved were the oculomotor nerves followed by the fifth cranial nerve, the facial nerve and other lower motor cranial nerves. The olfactory and auditory nerves were spared except for one case with slightly diminished speech discrimination. Florid proptosis and orbital oedema were not seen, and might suggest another diagnosis such as cavernous sinus thrombosis.

Corticosteroid medication resulted in rapid amelioration of pain but it was less certain that resolution of cranial nerve deficits was hastened. The problem recurred in 4 patients but permanent deficits were rare. Laboratory tests were unrevealing except for mild elevation of the CSF protein content with pleocytosis in some cases. Full neuroradiological investigation was necessary to exclude tumours, aneurysms or treatable inflammatory processes.

The patients with multiple cranial neuropathy showed almost identical clinical symptoms to those who have been designated with the Tolosa-Hunt syndrome. Hunt (1976) proposed criteria for this syndrome consisting of (1) steady boring pain behind the eye; (2) cranial nerve dysfunction localized to the third, fourth, sixth, first division fifth and periarterial sympathetic fibres; (3) symptoms lasting days or weeks; (4) spontaneous remission and recurrence; and (5) absence of involvement of structures outside the cavernous sinus. Steroid-responsiveness was later emphasized (Smith and Taxdal, 1966). The only distinguishing criterion from multiple cranial neuropathy is therefore the requirement that structures involved be confined to the cavernous sinus. This appears arbitrary since otherwise typical cases of the Tolosa-Hunt syndrome have involved the facial nerve (Cohn *et al.*, 1979; Swerdlow, 1980; Vallat *et al.*, 1980; Inzitari *et al.*, 1981). Steele and Vasuvat (1970) also noted that their cases of multiple cranial neuropathy were similar to cases designated as the Tolosa-Hunt syndrome (Steele and Vasuvat 1970). The pathological features of the Tolosa-Hunt syndrome also overlap with those of orbital pseudotumour and orbital myositis, and some cases of otherwise typical Tolosa-Hunt syndrome have been associated with rather florid proptosis (Forrest, 1949; Rosenbaum *et al.*, 1979). The very minimal (and often incidental) pathological material available nevertheless suggests that at least a subgroup of cases with these syndromes may share a similar pathological process (e.g., subacute granulomatous inflammation) (Tolosa, 1954; Schatz and Farmer, 1972). This hypothesis, however, needs further pathological confirmation stemming from wider recognition of the clinical entity.

Some cases of multiple cranial neuropathy may represent oligosymptomatic forms of the Guillain-Barré syndrome. In 1938 Van Bogaert and Maere reported 3 patients in whom the Guillain-Barré syndrome was localized to the cranial nerves and 5 such cases were later reported by Munsat and Barnes (1965). Nevertheless, in their patients, pain was not a feature, and they frequently exhibited an ataxic gait and dysmetria in addition to cranial nerve palsies. The CSF showed typical albuminocytologic dissociation. Only one of our cases fits this category. Case 9 had a preceding viral illness, loss of reflexes with subsequent recovery, involvement of the oculomotor and trigeminal nerves and albuminocytologic dissociation. Throbbing bitemporal headaches which occurred during the illness were different in character from the unilateral constant boring pain experienced by most other patients.

Both mycoplasma and infectious mononucleosis have been reported to cause isolated cranial nerve abnormalities, but the syndrome of multiple cranial neuropathy has not been documented (Schnell *et al.*, 1966; Murray *et al.*, 1975; Grose *et al.*, 1975; Cassell and Cole, 1981). We encountered one case of multiple cranial neuropathies with apparent mycoplasma infection and none with infectious mononucleosis, despite review of all charts listed with either diagnosis. The case associated with apparent mycoplasma had several features which differed from the idiopathic cases. There was more CSF pleocytosis (up to 93 mononuclear cells/mm^3) and the headache was generalized and constant. Three of the idiopathic multiple cranial neuropathy cases had negative serological testing for mycoplasma.

Meningitis, especially when caused by fungi, tuberculosis or listeria, may present with headache and cranial nerve palsies, but the CSF findings are usually characteristic. Aspergillosis can evolve from an initial orbital or sinus infection into a superior orbital fissure syndrome and chronic basal meningitis (Beal *et al.*, 1982). A biopsy may be required to confirm the diagnosis.

Tumours may be difficult to exclude because they may cause local pain, followed by cranial nerve symptoms, and they are occasionally steroid-responsive. Steroid-responsive painful ophthalmoplegia has been reported with chordomas, giant-cell tumours, lymphomas and epidermoids (Thomas and Yoss, 1970; Fowler *et al.*, 1975; Kline and Galbraith, 1981). Meningiomas progress slowly and do not typically cause local pain. More difficult to exclude are nasopharyngeal tumours and chordomas, but radiological procedures usually demonstrate bony erosion. Our third Tolosa-Hunt case had bony erosion of the superior orbital fissure, a feature that gives rise to concern and which usually warrants further investigation, in some cases, biopsy. Erosion of the sella turcica has also been reported with the Tolosa-Hunt syndrome (Polsky *et al.*, 1978).

Carcinomatous meningitis may cause multiple cranial nerve signs. Features favouring this diagnosis are absence of pain, involvement of multiple sites along the neuraxis, involvement of the eighth cranial nerve, and characteristic CSF findings. In 20 cases with cranial nerve palsies at the onset seen at our hospital, only 5 had pain. This pain was typically a generalized headache, sometimes with associated neck pain.

Adour (1982) reported that some cases of Bell's palsy are accompanied by dysfunction of the vagal or trigeminal nerve but in our experience this was uncommon. Rarely vasculitis, particularly Wegener's granulomatosis, may cause multiple cranial neuropathy, but keratitis and involvement of other organs is typical (Cogan, 1955; Drachman, 1963). Sarcoidosis is also a consideration and involvement elsewhere in the body must be excluded. Aneurysms also must be excluded but it would be unusual for them to affect both oculomotor and lower cranial nerves. Ophthalmoplegic migraine can be differentiated by the frequent family history of migraine, a self-limited course, pulsatile headache and teichopsia (Hoes *et al.*, 1981). Cases have also been reported in association with dysglobulinaemia (Kreindler and Marcovei-Patrichi, 1968) and chronic glandular tuberculosis (Symonds, 1958; Victor and Adams, 1968). A parainfectious immune response must be considered, but in our cases a preceding history of a viral syndrome, immunization, or allergic reaction was uncommon. After all the above considerations, we find that 3 of our original cases cannot be considered strictly 'idiopathic'. Cases 9 and 15 were suggestive of the Guillain-Barré syndrome and mycoplasma infection respectively but, as discussed, both differed from the other cases. Tolosa-Hunt Case 2, with an ESR of 113 mm/h, could be an example of biopsy-negative giant cell arteritis.

Several features of all the remaining cases are compatible with herpes virus infection. Both herpes zoster and simplex have been associated with pain, cranial nerve palsies, granulomatous inflammation, recurrences and precipitation by stress (Aitken and Brain, 1933; Adour *et al.*, 1975; Magnussen and Patanella, 1979). Our first case showed an acute phase CSF herpes simplex titre of 1 : 128. This raises the possibility that in subgroups of patients with this syndrome, the morbid process is mediated by several viral agents. Pathophysiologically, an indolent multifocal pachymeningitis could explain many of the clinical features. Within this framework, further prospective virological and pathological investigations of future cases appears warranted.

It should be clear that recognition of the syndrome of acute multiple cranial neuropathy allows for few diagnostic shortcuts, given the aetiologically nonspecific nature of its presentation. Nevertheless, familiarity with this entity in the English literature will help clinicians to tailor a clinically focused approach aimed at elucidating its aetiology(ies). Diagnosing CNS viral infections using current laboratory techniques is cumbersome. For example, serological tests for herpes viruses may not be useful since reactivation in the CNS is not usually associated with an antibody response (Nahmias *et al.*, 1973). Some promising noninvasive, or tissue-dependent techniques in this field include simultaneous CSF and serum radioimmunosorbent assays, CSF lymphocyte immunofluorescence, passive haemagglutination techniques (controlling for the CSF/serum IgG index), and in situ hybridization for viral DNA/RNA (Nahmias and Roizman, 1973; Klapper *et al.*, 1981; Koskiniemi and Vaheri, 1982; Taylor *et al.*, 1984; Aksamit *et al.*, 1985; Brahic *et al.*, 1985). Using these newer techniques, it might be possible to consolidate and further clarify some of the clinicopathological entities within the idiopathic cranial polyneuropathy syndrome.

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CLINICAL CATEGORIES OF NEUROBRUCELLOSIS

A REPORT ON 19 CASES

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SUMMARY

Brucellosis rarely can present with involvement restricted to the nervous system. We describe a total of 19 cases of neurobrucellosis in whom the clinical presentation lay in three distinct categories. The first was an acute presentation with meningoencephalitis. The disease also presented in a chronic form where the brunt of the illness can either be in the peripheral or the central nervous system (CNS). The chronic peripheral form is that of a proximal polyradiculoneuropathy. The central form is that of diffuse CNS involvement, predominantly with myelitis or cerebellar involvement with or without cranial nerve palsies. Although the two chronic forms, 'peripheral' and 'central', are distinct, some overlap is possible. This was not observed for the acute form. The pathology of the three presentations may be different, being a direct effect of infection in the acute form, and an immune-related process, possibly demyelinating in nature, in the chronic forms. The response to treatment in the acute and chronic forms is also different, being much better in the acute form.

Awareness of the condition and performance of the appropriate serological tests will differentiate neurobrucellosis from other chronic CNS infections, especially tuberculosis and neurosyphilis.

INTRODUCTION

Involvement of the central nervous system (CNS) in systemic brucellosis (Mediterranean fever, Malta fever) is rare. The common symptoms of chronic brucellosis are headache and lassitude (Williams, 1982; Wright and Woodruff, 1984); neither of these symptoms is due to direct CNS infection. Direct CNS infection is quite rare (Williams, 1982; Young, 1983). The presentation of neurobrucellosis is diverse: several areas of the nervous system, both central and peripheral, can be involved. Meningitis, diffuse and localized encephalitis, myelitis, radiculoneuritis (Spink, 1956; Fincham *et al.*, 1963; Abramsky, 1977; Sahs, 1978), and cranial nerve involvement, including the second, seventh and eighth (Spink, 1956), are all described. Fincham *et al.* (1963) identified four general categories of presentation:

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a total of 9 cases was reported and the clinical categories were meningoencephalitis, subarachnoid haemorrhage, myelitis and peripheral neuritis. The most recent report described a total of 6 patients: no attempt was made at clinical categorization, perhaps because of the small number of patients (Bashir *et al.*, 1985). It has always been assumed that neurobrucellosis is due to the direct effect of the organism or its toxins.

All these diverse manifestations can lead to confusion and delay in diagnosis. It may also lead to difficulty in differentiating neurobrucellosis from other chronic infections, especially tuberculosis and syphilis, as the clinical presentations can be similar. We present our experience of neurobrucellosis in 19 cases treated in our institutions over a period of three years. We try to throw new light on the clinical categorization, pathophysiology, differential diagnosis and effects of therapy.

CLINICAL OBSERVATIONS

Over a period of three years, 19 cases of neurobrucellosis were diagnosed. They were divisible into three categories according to the duration of symptoms and the clinical state. All our patients had a history of exposure to raw milk from cows, goats or camels.

Cases 1 to 8 presented with an acute febrile illness with headache and signs of meningeal irritation. Five patients were unconscious during their illness, but only 1 required assisted ventilation (Case 1). Epileptic seizures occurred in 1 patient (Case 1). A focal neurological deficit (hemiparesis) and papilloedema with a sixth cranial nerve palsy were observed in 2 of these patients (Cases 3 and 7, respectively).

The other 11 patients presented in a more chronic manner. Neurological symptoms were present for at least three months in all. In 6 (Cases 9–14), the clinical presentation was mainly that of back pain and a flaccid paraparesis. Hypotonia and areflexia were universal. In addition to the clinical evidence, all 6 patients had electromyographic features of a proximal demyelinating polyradiculoneuropathy. In only 1 patient was axonal involvement noted (Case 10). The last group of 5 patients presented with a spastic paraplegia or cerebellar ataxia with deafness. One of these patients had electromyographic evidence of a proximal radiculoneuropathy (Case 17). Details of the clinical presentation of the patients are presented in Table 1, and further discussion on the clinical state is given below.

Clinical Categories

The three categories of neurobrucellosis that were defined are meningoencephalitis, polyradiculoneuropathy and diffuse CNS involvement.

Meningoencephalitis. This group comprises a total of 8 cases (Cases 1–8). The presentation was acute, with impairment of consciousness and obvious features of meningitis in most patients. The duration of symptoms before hospital admission was less than five days in 5 of the 8 patients. The CSF showed a lymphocytic cellular reaction in all 8 (*see* section on cerebrospinal fluid).

TABLE 1. CLINICAL PRESENTATION OF PATIENTS WITH NEUROBRUCELLOSIS

Case	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*	*19*
Age (yrs)	12	23	38	16	60	30	25	7	45	16	50	18	48	45	46	35	60	30	65
Sex	M	M	M	F	M	F	F	M	M	F	M	F	M	M	M	M	M	M	F
Headache	+	+	+	+	+	+	+	+											
Fever	+	+	+	+	+	+	+	+		+		+							
Meningeal signs	+	+	+	+	+	+	+	+											
Unconsciousness	+	+			+	+	+												
Papilloedema							+												
Seizures	+																	+	
Hemiparesis			+																
Back pain									+	+	+	+	+	+	+				
Flaccid paresis									+	+	+	+	+	+					
Areflexia									+	+	+	+	+	+					
Deafness												+				+	+	+	+
Cerebellar ataxia												+				+	+	+	+
Spasticity															+	+		+	+
Urinary retention														+	+	+		+	+

All patients made an uneventful recovery. Treatment was given for eight weeks (*see* section on therapy).

Proximal polyradiculoneuritis (*peripheral form*). This presentation was noted in 6 cases (Cases 9–14). The main presenting features were back pain, paraparesis and tendon areflexia. Two patients had lumbar radiculograms before referral to the neurology department (Cases 10, 11). Hypotonia and areflexia were universal in all patients in this group. No clinically detectable sensory impairment was noted in any of them. Myelography was performed in all 6 patients and revealed features of thoracic arachnoiditis in only 1 (Case 9). The CSF showed a moderately increased protein content and a lymphocytic reaction in all patients (*see* section on CSF results). An EMG was performed in all cases and confirmed proximal radicular involvement in each of them. There was appropriate delay in motor conduction, particularly in the lower limbs, with prolongation of F wave latencies. Sensory nerve conduction was normal in all cases. The single patient with clear evidence of axonal degeneration had slight slowing of motor conduction with prominent denervation activity on EMG. The course of the illness was chronic and improvement was already evident even before commencement of therapy in 1 patient (Case 12). Except for Case 11 who made a full recovery, all patients were left with minor disability.

Diffuse CNS involvement (*central form*). This was noted either as a myelitis with associated cranial nerve abnormalities or as a cerebellar syndrome, again with cranial nerve involvement. In the first variant, the presentation was that of a pure spastic motor weakness without sensory loss (Cases 15, 16, 18, 19). The picture was that of back pain followed by spastic paraparesis after two or three months. All patients developed spasticity, hyperreflexia, clonus and extensor plantar responses. There were no sensory signs and retention of urine developed in all. Three patients had bilateral sensorineural deafness with high tone deafness on audiometry and abnormal brainstem auditory evoked potentials (BSAEPs) (Cases 16, 18, 19). The visual evoked potentials (VEPs) were also prolonged from both eyes in 2 patients (Cases 16, 18). There were no signs of lower motor neuron involvement clinically. One patient (Case 18) had a history of an acute meningitis with unconsciousness a year before his paraparesis. He recovered in a week and was labelled as a case of 'lymphocytic meningitis' of undetermined origin. He went on to develop attacks of loss of consciousness which were considered to be postencephalitic epileptic seizures and was started on carbamazepine. Three patients with spastic paraplegia had signs of cerebellar involvement in both upper limbs (Cases 16, 18, 19). Electromyography showed no features of neuropathy. CSF examination again revealed a lymphocytic pleocytosis (*see* section on CSF results). Myelography was normal in the 4 patients with spasticity (Cases 15, 16, 18, 19).

Cerebellar ataxia and cranial nerve involvement were the two main presenting features in 1 patient (Case 17). The ataxia was associated with profound sensorineural deafness. This patient also had EMG evidence of a proximal polyradiculoneuropathy.

Mixed cases. There was no overlap between patients with acute and chronic presentations. None of the patients with meningoencephalitis developed a permanent neurological deficit. The patient (Case 18) mentioned above, who had a 'lymphocytic meningoencephalitis' a year before developing a paraparesis, could represent a 'chronic brucella meningitis' progressing to CNS involvement.

Some patients in the polyradiculoneuritis group had signs of possible or definite spinal cord involvement with absent abdominal reflexes (Case 9) and extensor plantar responses (Cases 13, 14). Cerebellar ataxia and deafness were noted in 1 patient (Case 12). On the other hand, in the central group Case 17; the patient with predominant cerebellar ataxia and profound deafness also had electrical evidence of a neuropathy.

Cerebrospinal Fluid

The combination of a moderate elevation of the protein content and a lymphocytic pleocytosis was almost universal (Table 2). The mean total protein concentration for all patients was 1.77 g/l (range 0.66–3.84). In the meningoencephalitis group the mean was 1.52 g/l (0.66-3.84), in the radiculoneuritis group, 1.92 g/l (0.93-3.10) and in the group with diffuse CNS involvement, 2.46 g/l (2.1-3.0). There was a pleocytosis in all cases in all categories except for Case 11. The mean cell count for all patients was 182 cells/μl (range 4–1200). For the meningoencephalitis category, the mean was 365 cells/μl (range 47-1200), for the peripheral (polyradiculoneuritis) group 83 cells/μl (4-372) and for the diffuse CNS (central) group, 97 cells/μl (24–226). The majority of cells were lymphocytes, mean 90.6% (range 70-100%). The sugar content was normal in the majority of cases. It was below 2 mmol/l in 5 cases, 3 in the meningoencephalitis group (Cases 4, 6, 8) and 2 in the peripheral group (Cases 12, 14). The IgG/albumin ratio for all patients was raised with a mean of 0.38 (range 0.29-0.51); there was no difference in the ratio between the three groups.

TABLE 2. CEREBROSPINAL FLUID FINDINGS IN THE DIFFERENT CATEGORIES OF PATIENTS WITH NEUROBRUCELLOSIS

Categories of patients	*No. of patients*	*CSF findings: mean (range)*		
		Protein (g/l)	*Cells/μl*	*(%) lymphocytes*
Acute miningoencephalitis	8	1.52 (0.66–3.84)	365 (47-1200)	88 (70-100)
Chronic peripheral	6	1.92 (0.93-3.10)	83 (4–372)	94 (85-100)
Chronic central	5	2.46 (2.10-3.00)	97 (24–226)	90 (70-100)
All groups	19	1.96 (0.66–3.84)	182 (4–1200)	90.60 (70-100)

In all cases Gram, India ink and Ziehl-Neelsen staining was performed. Routine bacterial culture (aerobic and anaerobic), as well as culture for acid fast bacilli, was also carried out. It was possible to culture *Brucella melitensis* in only 3 patients, all with meningoencephalitis: from the blood and CSF (Case 4), blood alone (Case 2) and CSF alone (Case 5).

Serology for syphilis in the CSF was negative in every case; the VDRL and TPHA were the two tests employed.

Serological Tests

Tube agglutination test for brucella was carried out in serum in all patients and showed a significant titre of at least 1:320 in every case. The enzyme linked immunosorbent assay (ELISA) was performed for detection of brucella-specific immunoglobulins in 11 cases, 4 in meningoencephalitis group (Cases 2, 5, 7, 8), 3 in the peripheral group (Cases 12, 13, 14) and 4 in the central group (Cases 16, 17, 18, 19). The ELISA titres for brucella-specific IgG, IgM and IgA were significantly elevated in the serum of all tested patients. Nine of the 11 patients had CSF as well as serum ELISA, 3 in the meningoencephalitis group (Cases 5, 7, 8), 3 in the peripheral group (Cases 12, 13, 14) and 3 in the central group (Cases 17, 18, 19). In the CSF, the brucella-specific IgG reciprocal titre was 12800 in 8 patients and 6400 in 1. The IgM titre was significantly elevated in 6 patients ($\geqslant 200$) and negative in the CSF from 3 patients (Cases 5, 14, 17). In addition, all patients had a significant CSF IgA titre of $\geqslant 400$ or more except in 2 patients (Cases 5, 17).

Haematological Studies

A full blood count was performed on every patient. The mean values obtained were: Hb 12.4 g/dl (range 10.1–16.2); WBC 6.5×10^9/l (range 4.7–11.2), lymphocytes 45% (range 29–57); ESR 22 mm/h (range 5–50).

Radiological Investigations

A chest radiograph was taken in every case and was normal in all patients except for those who were unconscious during the early part of their illness (meningoencephalitis group) when changes related to congestion and aspiration were noted. No evidence of tuberculosis was detected in any patient. Cranial CT scanning was undertaken in all cases in all three groups. Brain oedema was noted in 2 cases, but only during the acute phase (Cases 3, 7).

Spine radiographs and metrizamide myelography were performed in all cases from the second and third groups. One patient (Case 9), who clinically had a polyradiculoneuropathy, had features of thoracolumbar arachnoiditis. No evidence of skeletal involvement was noted on bone scanning except for increased tracer uptake in the lumbar region in 1 patient (Case 13).

Other Investigations

All patients who had a history of fever had tests for typhoid fever (Widal), toxoplasmosis (indirect fluorescence), infectious mononucleosis (monospot) and examination of blood films for malaria. These were performed in all the meningoencephalitis group and some of the patients in other groups. None of these tests was positive. Nearly all our patients had a positive Tine test. No evidence of active tuberculosis was found.

Treatment

All our patients received eight weeks' treatment with tetracycline and a shorter course of streptomycin except for those with symptoms referable to the eighth cranial nerve where streptomycin was omitted. Cotrimoxazole (sulphamethoxysasol and trimethoprim) was given to all cases for eight weeks. Rifampicin was used in 9 cases, 4 in the meningoencephalitis group (Cases 3, 4, 7, 8), 2 in the polyradiculoneuritis group (Cases 12, 14), and 3 in the central group (Cases 16, 18, 19). Corticosteroids (prednisolone) as a short eight weeks course were used in 8 patients, 3 in the peripheral group (Cases 9, 12, 14) and the 5 in the central group. Dexamethasone was used in only 1 case, who was in the meningoencephalitis group (Case 7). In those patients without or with only partial improvement, a second course of tetracycline and rifampicin was given for a further two months.

Outcome

All the patients in the meningoencephalitis group recovered completely within a short period of one to two weeks. No neurological deficit was noted. In 1 patient infection outside the nervous system in the form of orchitis appeared three months later (Case 1). One patient had a neurological deficit before treatment and that totally cleared (Case 3). Another patient had epileptic seizures during the early phase which never recurred; his anticonvulsants were stopped a year after his illness (Case 1). Generalized brucellosis was known to be present in only 1 patient before presentation (Case 6).

In patients with predominant peripheral involvement, the outcome was reasonable. One patient only made a total recovery (Case 11). The rest improved but were left with a minor degree of disability.

The worst group were those patients with diffuse CNS disease. One patient was able to return to work but remained with signs of spastic paraparesis (Case 15). Another partially improved in that his deafness and ataxia nearly disappeared; BSAEPs returned to normal (Case 18). Another 2 patients (Cases 16, 17) showed no appreciable improvement. In spite of a second course of treatment most patients remained with marked disability (Cases 16, 17, 18, 19). A response to treatment resembling a Jarisch-Herxheimer reaction was encountered in 3 patients: 1 in the peripheral group (Case 12) and 2 in the central group (Cases 16, 19). This febrile reaction settled spontaneously without the need to discontinue therapy.

DISCUSSION

Neurobrucellosis is rare and, overall, is decreasing in incidence (Wright and Woodruff, 1984). In general reviews of brucellosis, the neurological manifestations have received only minor comment (Young, 1983). We have encountered our cases over a period of three years. Data from the Department of Preventative Medicine in the Ministry of Health (Health Statistics Annual Report, 1984) show that there is a rising incidence of brucellosis in Kuwait. A total of 732 cases were reported in 1984 with an incidence rate of 42.78/100000 compared with 12 cases in 1976 with an incidence of 1.15/100000 population. This may not represent the true incidence because it was based on patients seeking medical advice for symptoms related to brucellosis and in whom the diagnosis was confirmed by serological tests. Actual CNS involvement has been reported to be in the order of 10% (Spink, 1956) to 25% (Abramsky, 1977). The latter author reported on a total of 24 cases of generalized brucellosis, 6 of whom had neurological involvement. Taking into account the total, probably underestimated, figure for the incidence of brucellosis in Kuwait and the number of our patients, a realistic figure for actual CNS involvement in brucellosis lies between 3 and 5% of all cases.

Since the end of the last century several authoritative and detailed analyses of neurological involvement in brucellosis have been reported. The manifestations are diverse: several different parts of the nervous system may be involved (Sahs, 1978). In a report from a single institution (Fincham *et al.*, 1963), a total of 9 cases was documented and an arbitrary grouping of these diverse manifestations into four main groups was made. These included meningoencephalitis, subarachnoid haemorrhage, myelitis and myelopathy, and neuritis (cranial and peripheral). There was no clear indication of the mode of presentation, progress, response to treatment or outcome, nor was there speculation as to the pathological processes in each of the clinical categories.

We have tried to simplify the picture by dividing the clinical presentation of neurobrucellosis into two main large categories according to the mode of presentation of the illness. In the acute category, the syndrome is that of meningoencephalitis with a short duration of generalized symptoms associated with signs of diffuse cerebral involvement resulting in coma, respiratory depression and some cases of epileptic seizures. A clear history of generalized brucellosis was noted in only 1 of the 8 patients and here inadequate therapy was given.

Meningoencephalitis has been a well recognized mode of presentation of neurobrucellosis (Nichols, 1951; Fincham *et al.*, 1963; Abramsky, 1977; Larbrisseau *et al.*, 1978; Bashir *et al.*, 1985). We believe that the pathology of meningoencephalitis is that of a direct effect of the organism or its products on the meninges and brain. However, meningoencephalitis can be the initial manifestation of brucellosis or an acute superimposed phenomenon in a patient who has chronic generalized brucellosis.

The response to treatment was dramatic in the acute group. Even patients who were unconscious and on a ventilator recovered totally within a few days. This response in some patients was so rapid that it made us question whether the treatment or the natural history of the disease was responsible. We have not tried to withhold treatment over the acute stage and observe the outcome but certainly 1 of our patients recovered consciousness before starting appropriate antibrucella therapy.

Chronic meningitis due to brucellosis has been described (Singh *et al.*, 1974; Strannegard *et al.*, 1985). Both reports were on single cases. The patients indeed had symptoms of two and one years, respectively, before the diagnosis of brucella meningitis was confirmed by CSF culture, but no conclusive evidence was given of brucella infection prior to the final diagnosis and it is therefore only speculative that the previous symptoms were due to 'chronic brucella meningitis'. One of our patients had a 'lymphocytic meningitis' a year before his presentation with CNS involvement.

In the chronic polyradiculoneuritis category the weakness was noted only in the legs. The involvement was purely motor in all cases. This has been documented previously, when a picture similar to anterior poliomyelitis was reported (Debono, 1964). Electromyography confirmed the presence of a proximal demyelinating neuropathy in all cases except 1 where axonal degeneration was noted. Myelography showed features of arachnoiditis in 1 patient, being normal in the rest. Arachnoiditis has been well documented previously (Sahadevan *et al.*, 1968).

In the central category 4 patients had a spastic paraplegia and 1 severe cerebellar ataxia. Cases of myelitis have been recorded previously (Fincham *et al.*, 1963; Larbrisseau *et al.*, 1978) and cerebellar ataxia is also recognized (Sahs, 1978).

In the central category, cranial nerve involvement was noted. Four patients had sensorineural deafness and 2 had abnormal visual evoked potentials. Eighth nerve involvement is well recognized (Spink, 1956; Bashir *et al.*, 1985). Papilloedema and optic neuritis have also been reported (Green, 1939). To our knowledge this is the first case report of prolonged VEPs in a patient with neurobrucellosis without associated ocular symptoms or signs. This finding may possibly be due to demyelination. Peripheral nerve as well as corticospinal tracts and circumferential areas of the spinal cord have been shown to be demyelinated at autopsy (Fincham *et al.*, 1963). We did not encounter any case of cerebrovascular involvement leading to subarachnoid haemorrhage as has been reported previously (Fincham *et al.*, 1963).

Peripheral blood examination was not valuable in giving guidance as to the nature of the illness: neither the differential white cell count nor the ESR were helpful.

Examination of the CSF was abnormal in some aspect in all patients in all three groups with a moderate elevation in protein content and a lymphocytic pleocytosis. In some cases there was a high IgG/albumin ratio. Unfortunately tests for oligoclonal IgG bands were not available to us but they have been detected in neurobrucellosis (Silva *et al.*, 1980). In only 3 cases, all in the meningoencephalitis group, was *Brucella melitensis* cultured from either the CSF and/or the blood. This low yield is well recognized (Sahs, 1978). The use of ELISA on serum for the diagnosis of brucellosis has been reported (Sippel *et al.*, 1982). We in addition have used ELISA on CSF and this showed significant titres in all cases. We have recently established that CSF ELISA is a sensitive and specific test for the rapid diagnosis of neurobrucellosis (Araj *et al.*, 1986). The value of brucella-specific immunoglobulins in the CSF in relation to the stage of the disease and improvement remains to be elucidated. However, a reduction in the CSF brucella titre with clinical improvement in a case of meningoencephalitis has been reported (Strannegard *et al.*, 1985).

In a recent review of brucellosis, tetracycline (2 g daily) with streptomycin (1 g daily) for three weeks were recommended for therapy (Wright and Woodruff, 1984).

Other workers have reported the use of a similar regimen with good results (Samra *et al.*, 1983). Trimethoprim-sulphamethoxazole (cotrimoxazole) has also been reported to be useful in treatment (Giunchi *et al.*, 1971). More recently rifampicin has been recommended (Llorens-Terol and Busquets, 1980). Young (1983), commenting on the difficulty of treating neurobrucellosis with all the above mentioned drugs, suggested the use of intravenous moxalactam, a third generation cephalosporin, in addition to rifampicin, for six weeks. The most recent report on neurobrucellosis recommended the use of cotrimoxazol and rifampicin for three months (Bashir *et al.*, 1985). As was observed in 3 of our patients, a reaction similar to the Jarisch-Herxheimer reaction has been reported (Young, 1983).

The treatment of neurobrucellosis thus remains controversial. We have used tetracycline, cotrimoxazole, streptomycin (except when contraindicated) and rifampicin. Corticosteroids were used only in patients with arachnoiditis, cranial nerve involvement or spinal cord pathology. Treatment was maintained for at least eight weeks. We are unable from this study to suggest a specific course of treatment, but it is obvious that prolonged courses of three to four months may be necessary in the chronic central category.

The type of presentation, the progress of the disease, the response or lack of it to treatment, the multiple involvement of various parts of the nervous system, the presence of an immune reaction in the CSF, and the previous reports of a demyelinating process, all make us postulate that, perhaps the rather acute meningoencephalitic syndrome is due to a direct effect of the brucella organism on the nervous system. The chronic form, however, might be due to persistent intracellular effects of the organism or perhaps the bacterial infection might trigger an immune mechanism leading to demyelination which could be responsible for, if not all, at least part of the pathology.

It suffices to say that a patient who has a history of paraparesis for over a year, abnormal VEPs and BSAEPs, a raised CSF protein content with slight lymphocytosis and oligoclonal IgG bands could well be suspected of having multiple sclerosis if the appropriate brucella serological tests are not performed.

In conclusion, neurobrucellosis is still a problem, at least in Middle Eastern countries. The exact pathology of various aspects of the illness is still not totally resolved: an additional demyelinating process is possible to account for some of the features. The use of ELISA on CSF has been shown to be helpful in diagnosis. Treatment is still not ideal for those with the chronic forms of the disease. Further work is required to elucidate the immunological aspects of the illness and try to find better and easier methods of therapy.

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ALLOAESTHESIA

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SUMMARY

Alloaesthesia is a condition in which a sensory stimulus given on one side of the body is perceived at the corresponding area on the other side. We observed this in 20 out of 123 patients with hypertensive cerebral haemorrhage in the acute stage (within twenty days), all except 1 in the right hemisphere. This phenomenon was observed in 17 out of 35 patients with right putaminal haemorrhage and only 1 out of 30 patients with right thalamic haemorrhage, suggesting it may be useful in differentiating putaminal from thalamic haemorrhage in the right hemisphere.

Three patients, with cervical tumour, cervical disc herniation and multiple sclerosis also showed alloaethesia. They had anterolateral lesions of the spinal cord. The cerebral and spinal cord lesions presented similar symptomatic characteristics of alloaesthesia.

It is suggested that as alloaesthesia is produced by noxious stimuli not only in spinal cord but also in cerebral lesions it may represent an elementary sensory disturbance of sensory pathways, and not a higher cortical dysfunction.

INTRODUCTION

Alloaesthesia is a peculiar symptom in which a sensory stimulus given on one side of the body is perceived on the other side at the corresponding area. Obersteiner (1880, 1881) first described it in patients with spinal cord lesions and with hysteria. By the beginning of this century, most of the reported cases were of tabes dorsalis and hysteria. Later, several cases with organic cerebral lesions were reported. More recently, neurologists have shown little interest in alloaesthesia, and for the past three decades few reports on it have appeared.

We found alloaesthesia in the acute stage of right putaminal haemorrhage, as well as in anterolateral spinal cord lesions. The aim of this study is to clarify the characteristics of the symptomatology of alloaesthesia and the sites associated with it as an aid to elucidating its mechanism.

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PATIENTS

Cerebral Lesions

Twenty cases of alloaesthesia were found and studied among 123 patients with hypertensive cerebral haemorrage diagnosed by computed tomographic (CT) scanning. They were all admitted to Chiba Emergency Medical Center between August 1980 and December 1982.

Spinal Cord Lesions

Three cases of spinal cord lesions (cervical tumour, cervical disc herniation and multiple sclerosis), showing alloaesthesia, were confirmed by metrizamide-enhanced CT scanning and/or magnetic resonance imaging (MRI). They were admitted to the Department of Neurology, Chiba University.

METHODS

Strong painful stimuli (pinching) were given on the nipples, the abdomen, the back, the hips, the upper and lower limbs and the patients' responses to these stimuli were observed.

We studied the types of stimulus which produced alloaesthesia, the areas of the body where alloaesthesia was produced, and the course of alloaesthesia. The patients were requested to report the areas where stimuli were applied and to point to them. Their responses with their eyes open and closed were observed.

In cerebral lesions, other higher cerebral dysfunctions, such as unilateral neglect (bisection of a line, copying the picture of a flower and the Albert line-crossing test), constructional apraxia (copying a diamond-shaped figure, a Greek cross and a cube), anosognosia, hemisomatagnosia, ideomotor apraxia, ideational apraxia, visual alloaesthesia and auditory alloaesthesia were examined. From the CT scan, we calculated the areas of the haemorrhage as they appeared on the different slices and obtained the volume of the haematoma (excluding intraventricular blood).

RESULTS

Localization

Cerebral lesions. Alloaesthesia was observed in 17 out of 35 patients with right putaminal haemorrhage, in 1 out of 30 patients with left putaminal haemorrhage,

TABLE 1. LOCALIZATION OF CEREBRAL LESIONS WITH ALLOAESTHESIA

	Cases with alloaesthesia	*Total cases*
Putaminal haemorrhage		
Right	17	35
Left	1	30
Thalamic haemorrhage		
Right	1	29
Left	0	8
Combined putaminal/ thalamic haemorrhage		
Right	1	6
Left	0	15
Total	20	123

in 1 out of 29 patients with right thalamic haemorrhage and in 1 out of 6 patients with right combined putaminal/thalamic haemorrhage. None of the 8 patients with left thalamic haemorhage or 15 patients with left combined haemorrhage showed alloaesthesia (Table 1).

Table 2 details the clinical manifestations of the 20 patients with alloaesthesia with cerebral lesions. All 20 patients were right-handed.

The volume of the haematoma in the patients with alloaesthesia ranged from 20 ml to 104 ml, the average volume in those with right putaminal haemorrhage being 42 ml. Surgical evacuation was performed on 6 out of 17 patients with right putaminal haemorrhage.

TABLE 2. CLINICAL DATA OF 20 CASES OF ALLOAESTHESIA WITH CEREBRAL LESIONS[1]

Cases[1]	*Alloaesthesia*[2]		*Period of disturbance of consciousness (days)*	*Accompanying higher cortical dysfunction*	*Localization*	*Volume of haematoma (ml)*	*Operation*
	Not felt as the expected sensation	*Duration (days)*					
1. N.N.	Pain	18	1	Anosognosia	R putamen	72	+
2. T.S.	Pain	3	10	—	R putamen	24	—
3. T.Y.	Itching	13	3	Anosognosia	R putamen	65	+
4. H.H.	Discomfort	8 >	2	Anosognosia	R putamen	28	—
5. K.I.	Discomfort	7 <	1	Anosognosia	R putamen	20	—
6. K.Y.	Discomfort	5	5	Anosognosia	R putamen	38	—
7. N.M.	Pain	5	9	—	R putamen	40	—
8. S.I.	Numbness	5	5	—	R putamen	28	—
9. K.K.	Numbness	12	5	Anosognosia	R putamen	20	—
10. N.Y.	Numbness	15	1	—	R putamen	32	+
11. T.S.	Discomfort	4	10	Anosognosia	R putamen	29	—
12. I.N.	Numbness	10	4	—	R putamen	54	+
13. K.N.	Discomfort	6	6	—	R putamen	104	—
14. G.M.	Discomfort	18	10	Anosognosia	R putamen	56	+
15. M.W.	Numbness	3	—	?	R putamen	29	—
16. S.Z.	Discomfort	1 <	5	?	R putamen	22	—
17. T.K.	Discomfort	2 <	5	?	R putamen	48	+
18. M.T.	Discomfort	5	5	Anosognosia	R thalamus	20	+
19. Y.Y.	Discomfort	1	—	?	combined putamen/thalamus	65	—
20. T.S.	Discomfort	14 <	7	—	L putamen	20	—

[1] All patients were right-handed. [2] To noxious stimuli.

Spinal cord lesions. All 3 patients had anterolateral cervical lesions. The patient with a cervical tumour (Case 21) had an anterolateral lesion at the right side of C3 segment. Alloaesthesia was found on the left side of the body from the upper abdomen to the knee. The patient with cervical disc herniation (Case 22) had an anterolateral lesion at the left side of C6–7 segments. Alloaesthesia was found on the right side of the body from the chest to the knee. The patient with multiple sclerosis (Case 23) had an anterolateral lesion at the left side of C6 segment. Alloaesthesia was found on the right side of the body from the upper to the lower abdomen.

Table 3 shows details of clinical manifestations of these 3 patients.

TABLE 3. CLINICAL DATA OF 3 CASES OF ALLOAESTHESIA WITH SPINAL CORD LESIONS

	Alloaesthesia			
Case	*Nature of stimuli*	*Not felt as the expected sensation*	*Motor deficits*	*Accompanying sensory disturbances*
21	Noxious	Discomfort	R hemiparesis	Severe loss to all stimuli R C3–4 Heat, cold and pin prick at and below L C4
22	Noxious	Discomfort	L hemiparesis	Heat, cold and pin prick at and below R C7
23	Noxious	Discomfort	—	Heat, cold and pin prick L C6

All patients were right-handed.

Clinical Characteristics of Alloaesthesia

All 23 patients, with both cerebral and spinal cord lesions showed very similar clinical characteristics as follows: (1) noxious stimuli (a sharp pinch, ice-cold water, pin prick) given on the side of hemisensory disturbance were perceived with a delay of about half a second at the corresponding area of the other side. Sometimes other stimuli such as vibration produced alloaesthesia; (2) the noxious stimuli were felt as different from sensations normally produced by such stimuli (discomfort, numbness, itching); (3) alloaesthesia frequently appeared in the trunk and the proximal part of the limbs and seldom appeared in the face and distal part of the limbs; (4) the area indicated by the patient corresponded exactly to that reported verbally; (5) the patients showed the same response with their eyes open or closed. We found two additional characteristics in the patients with cerebral lesions. (1) Alloaesthesia referred to the corresponding area on the opposite side of the body gradually disappeared in the recovery period, during which a disturbance in localizing the stimulated site was observed on the ipsilateral side. (2) Alloaesthesia appeared in the acute stage when there was a slight impairment of consciousness; it often continued after consciousness became clear and finally disappeared within twenty days.

ILLUSTRATIVE CASE REPORTS

Case 14. Cerebral Lesion

A 52-year-old right-handed man with a ten-year history of hypertension was found on the floor of his house with a left hemiplegia. One and a half hours later, he was admitted to Chiba Emergency Medical Center. A CT scan (fig. 1) revealed a medium-sized right putaminal haemorrhage (56 ml) with a slight midline shift. Three hours later, the haematoma was evacuated, after which his clinical state improved.

Neurological findings (day 3). There was slight impairment of consciousness (Glasgow Coma Scale (GCS), 14/15). Visual acuity and the visual fields on confrontation were normal; the pupils were

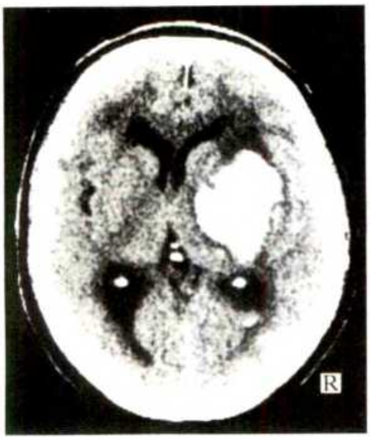

FIG. 1. CT scan on day 1 (*Case 14*), showing a medium-sized right putaminal haemorrhage (56 ml) with a slight midline shift.

equal and reacted to light. Extraocular movements were also normal; sustained conjugate deviation was not present. There was a left hemiplegia but muscle tone normal. Muscle stretch reflexes were hyperactive with an extensor plantar response on the left, and reflexes of spinal automatism were elicited by pin prick stimuli on the left shin and foot. There were severe deficits to touch, pin prick, heat, cold, vibration, and joint sensation on the left side of the body.

Alloaesthesia (day 3) (fig. 2A). The patient first showed confusion with regard to sharp pinching stimuli on the left side of the body. With a delay of about half a second, he reported uncomfortable sensations over the corresponding area on the right side, to which he pointed. Those areas included the nipple, the upper abdomen, the back, the hip and the proximal part of the arm. When the distal part of the left arm was pinched, he pointed to and reported discomfort in the left thigh. But when the left half of the face and left leg were pinched, he pointed to and reported a pain at the exact place where the stimulus was applied. The areas indicated corresponded exactly to those reported verbally. His reaction was the same with eyes open or closed.

His reactions to touch, pin prick, heat, cold, vibration, joint position and strong pinch applied on the right side of the body were immediate and localization of the area stimulated was accurate.

Neuropsychological findings (from days 3–14). Speech, reading and writing were normal. Hemiasomatognosia and unilateral neglect were not evident, but anosognosia for paralysis was present (on day 6). There was no constructional, ideomotor or ideational apraxia, or visual or auditory alloaesthesia.

Course of alloaesthesia. (On day 14) (fig. 2B) he was fully conscious. Sensory disturbances on the left side were steadily improving. Pin prick, heat and cold were perceived as 50–70% and vibration about 70% of that on the right side. Joint position sense, however, was absent on the left.

To a strong pinch on the left nipple and the upper abdomen, he responded accurately. After a delay of about half a second, he pointed to and reported discomfort over the corresponding contralateral area. When the left hip was pinched, he pointed to the left back. When the left upper and lower extremities were pinched, he pointed to their more distal parts. But when the left half of the face, the lower abdomen and the back were pinched, he pointed to and reported a pain at the exactly equivalent place.

Reactions to stimuli over the right side of the body were quick and accurate. Anosognosia disappeared.

Alloaesthesia referred to the corresponding contralateral area gradually disappeared and was replaced by an ipsilateral disturbance in localizing the stimulated site. After the eighteenth day, alloaesthesia disappeared completely.

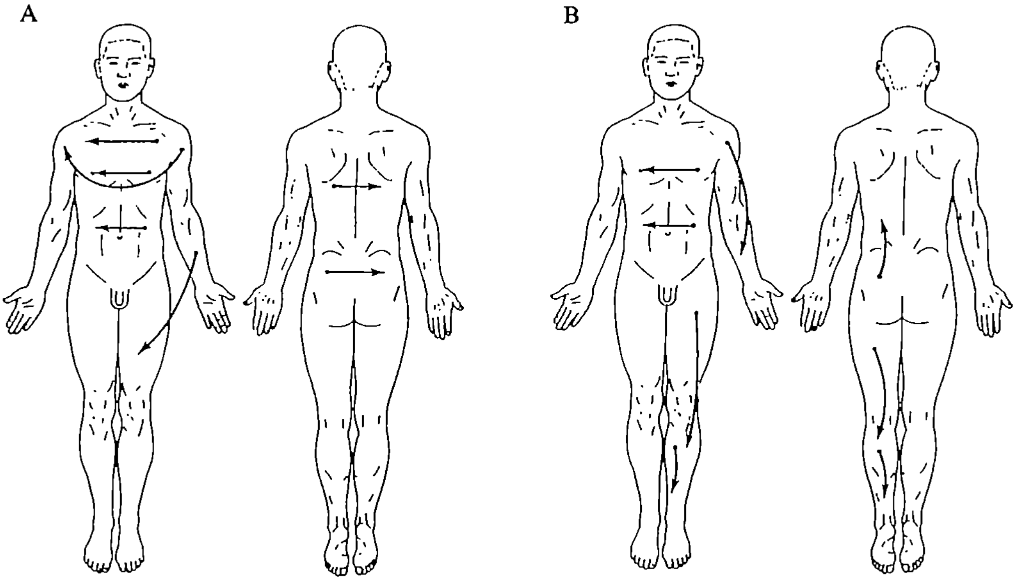

FIG. 2. Alloaesthesia produced by noxious stimuli (*Case 14*). A, on day 3. To sharp pinching stimuli on the left side of the body the patient reported discomfort with a delay of about half a second over the corresponding area on the right side, to which he pointed. B, on day 14. On sharp pinching of the left nipple and upper abdomen, he pointed to and reported, with a delay of about half a second, discomfort over the corresponding area on the right. When the left hip was pinched, he pointed to the left back. When the left upper and lower extremities were pinched, he pointed to their more distal parts.

Patient 21. Spinal Cord Lesion

A 49-year-old right-handed woman noted gradual onset of numbness in the right hand and foot in April 1981. In February 1982, she developed weakness in the right upper and lower extremities and a slight change in temperature sensation in the left half of the body while taking a bath. Because of further deterioration, she was admitted to the Department of Neurology, Chiba University Hospital on October 2, 1982.

Plain and tomographic cervical x-rays were normal. The metrizamide-enhanced CT scan (fig. 3) showed swelling of the spinal cord particularly in the right anterior part at C3–4 level indicating a spinal cord tumour.

Neurological findings on admission. She was fully conscious. The cranial nerves were normal. There was a right hemiparesis and spasticity of the right leg; muscle stretch reflexes were hyperactive with an extensor plantar response on the right. Abdominal skin reflexes were absent bilaterally. Co-ordination was normal. Fig. 4A shows the area of diminution in sensibility. Sensation for touch, pin prick, heat and cold was severely disturbed around the right shoulder. At and below the left C4 segment, there was sensory loss for heat, cold and pin prick. There was a slight deficit in touch and vibration at the right clavicular level and below. There was no loss of joint sensation. Urinary and bowel functions were normal.

Alloaesthesia (fig. 4B). Noxious stimuli (a sharp pinch, ice-cold water and electrical stimuli) applied on the left side of the body from the upper abdomen to the knee were perceived as discomfort over the corresponding area on the right side. The stimuli were perceived with a delay of about half a second. The same reaction occurred with the eyes open or closed.

Reaction to touch, pin prick, heat, cold, vibration, passive movement of the joint and strong pinch applied to the right side of the body were immediate and accurate.

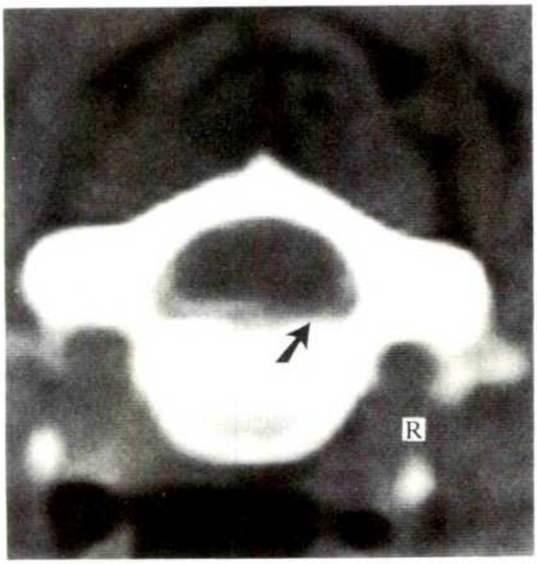

FIG. 3. Metrizamide-enhanced CT scan at C3–4 level (*Case 21*), showing a swelling of the spinal cord, greater anteriorly on the right, indicating a spinal cord tumour (arrow).

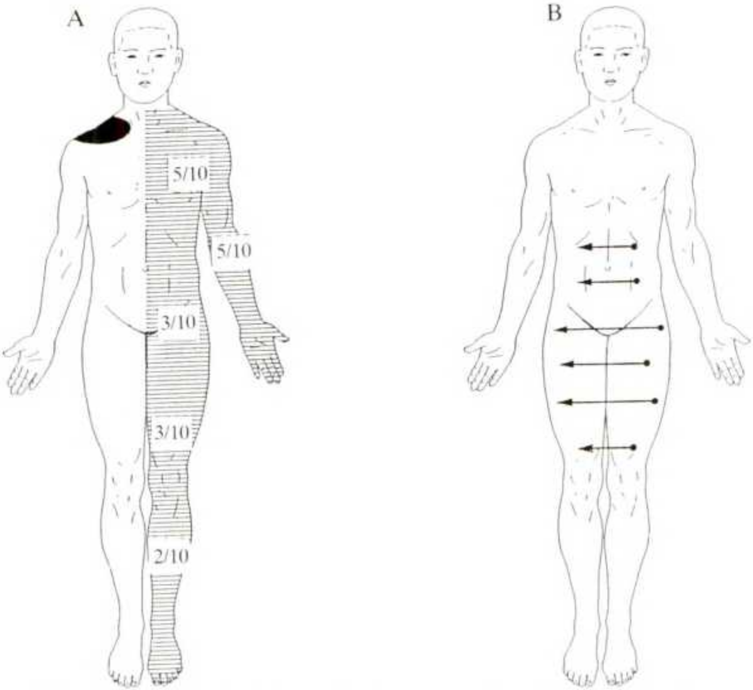

FIG. 4. Alloaesthesia produced by noxious stimuli (*Case 21*). A, sensation to touch, pin prick, heat and cold was severely disturbed around the right shoulder (black area). At and below the left C4 segment (cross-hatched), there was sensory loss for heat, cold and pin prick. The approximate severity of the loss on a scale of 0–10 is indicated on the figure. B, the noxious stimuli applied to the left side of the body from the upper abdomen to the knee were perceived as discomfort over the corresponding area on the right side.

Surgical operation and follow-up. On December 1, 1982, a rounded intramedullary tumour 1 cm in diameter was removed from the right anterolateral part of C3 segment. After operation, the neurological findings and alloaesthesia remained essentially unchanged.

DISCUSSION

Symptomatology

Table 4 shows 20 patients reported in the literature with alloaesthesia due to cerebral lesions. In only 2 of them (Bosc, 1892; Hécaen and de Ajuriaguerra, 1952) stimuli were perceived after a slight delay. In only 3 (Kramer, 1915; Schilder 1950; Hécaen and de Ajuriaguerra, 1952), were stimuli felt as different from the expected response. Alloaesthesia in the reported patients could be elicited by almost all sensory modalities: touch, temperature, pain, vibration and movement; pain elicited alloaesthesia most frequently (11 out of 13). In Hécaen and de Ajuriaguerra's (1952) patient, only noxious stimuli elicited alloaesthesia. It is the most striking characteristic in our 20 patients that alloaesthesia was elicited most commonly by noxious stimuli. Among the neuropsychological symptoms, anosognosia was observed most often (6 patients) as in our patients. In Hécaen and de Ajuriaguerra's (1952) and our patients, alloaesthesia was observed transiently while consciousness was slightly impaired in the acute stage.

As discussed above, only a few such cases have been adequately analysed in the literature. But among all the reported patients the symptomatic characteristics of Hécaen and de Ajuriaguerra's (1952) patient alone are really similar to those of our patients with cerebral lesions.

Our 3 patients with alloaesthesia due to spinal cord lesions showed certain similar characteristics. In the literature, symptoms quite similar to those of our patients have been reported following cordotomy (Ray and Wolff, 1945; Nathan, 1956; Pecker and LeBeau, 1957; Buermann and Finney, 1965).

It is most striking that the characteristics of alloaesthesia associated with spinal cord lesions very much resemble those of our cases with cerebral lesions; that is, alloaesthesia was elicited by noxious stimuli on the side of hemisensory disturbance and noxious stimuli were perceived with a delay of about half a second as different sensations over the corresponding contralateral area.

Localization

The reported cases of cerebral lesions with alloaesthesia include 5 autopsy cases with extensive infarctions and tumours (Pinéas, 1926, 1931; von Stockert, 1934; Schilder, 1950). From these reported data, we cannot localize the lesions responsible for alloaesthesia.

Our patients with cerebral haemorrhage had lesions almost exclusively in the right hemisphere (19 : 1). Eight out of 9 patients in the literature with unilateral hemisphere lesions also had right-sided lesions.

We observed alloaesthesia much more frequently in putaminal than in thalamic

TABLE 4. 20 CASES OF ALLOAESTHESIA IN THE LITERATURE WITH CEREBRAL LESIONS

		Alloaesthesia							
Reported cases	*Handedness*	*Nature of stimuli*	*Perceived with some delay*	*Not felt as the expected sensation*	*Disturbance of consciousness*	*Accompanying higher cortical dysfunctions*	*Cause*	*Localization*	*Autopsy*
Bosc (1892)	?	Pain, heat	+	?	?	?	CVD	R cerebral	—
Kramer (1915)	?	?	?	?	?	Anosognosia	CVD	R cerebral	—
Kramer (1917)	?	Pain, heat, noxious	?	+	—	?	CVD	Brainstem	—
Barré *et al.* (1923)	?	Touch	?	?	—	Anosognosia	CVD	R cerebral	—
Schilder (1923)	?	Pain, heat, cold, vibration, movement	?	+	?	?	CVD	Bilat. cerebral	—
Pinéas (1926)	?	Pain	?	?	?	Anosognosia	Infarction	R frontoparietal	+
		Pain	?	?	?	Anosognosia	Infarction	R cerebral (diffuse)	+
Pinéas (1931)	?	Touch, pain	?	?	?	Hemisomatagnosia	Infarction	R parieto-occipital	+
von Stockert (1934)	?	Touch, pain	?	?	?	?	Infarction	L temporo-occipital	+
Chavany and Houdart (1946)	?	Pain	?	?	?	Anosognosia Hemisomatagnosia	CVD	R cerebral	—
Bender *et al.* (1948)	?	?	?	?	—	Extinction	Atrophy	Bilat. cerebral	—
Bender *et al.* (1949)	Right	All stim.	?	?	—	Extinction	Atrophy	Bilat. cerebral	—
Bender and Nathanson (1950)	Right	Pain, vibration	?	?	—	Extinction	Atrophy	Bilat. cerebral	—
Schilder (1950)	Right	Touch, pain	?	?	Slight	?	Tumour	Bilat. cerebral	+
Hécaen and de Ajuriaguerra (1952)	Right	Noxious	+	Burning sensation	Slight	Anosognosia Hemisomatagnosia	CVD	R cerebral	—

CVD = Cerebrovascular disease.

haemorrhage (18 : 1). It may therefore be useful in differentiating them in the right hemisphere. In our observations, alloaesthesia was associated with haemorrhage of medium volume (mean 42 ml), which usually required evacuation. Although putaminal haemorrhage is common, alloaesthesia has not been reported, perhaps because in putaminal haemorrhage it occurs only transiently in the acute stage.

In the spinal cord lesions, all of our patients with alloaesthesia had anterolateral spinal cord lesions. In the literature, cases with alloaesthesia following cordotomy also had anterolateral lesions (Ray and Wolff, 1945; Nathan, 1956; Pecker and LeBeau, 1957; Buermann and Finney, 1965).

Mechanisms

Alloaesthesia with cerebral lesions has been considered to be due to higher cortical dysfunction, especially when accompanied by right parietal signs: anosognosia, extinction, hemineglect. Schilder (1923, 1950) considered it to be a dysfunction of the body schema, Bender *et al.* (1948, 1949, 1950) favoured a mechanism similar to extinction, and Watson *et al.* (1974) and Heilman and Valenstein (1985) a sensory response to the neglect syndrome. Some of our patients showed such right parietal signs as anosognosia besides alloaesthesia but others did not. Alloaesthesia also occurred with a left hemisphere lesion in a right-handed patient. Most of our patients with left cerebral haemorrhage had aphasia in the acute stage, and it is quite difficult to establish whether the patients had alloaesthesia or not. Therefore we cannot deny the existence of alloaesthesia even in left putaminal haemorrhage. The characteristics of alloaesthesia in our patients with spinal cord lesions are quite similar to those observed in our patients with hypertensive cerebral haemorrage. This disproves the view that alloaesthesia occurs only as a result of higher cortical dysfunction.

As indicated in fig. 5, Ray and Wolff (1945) attempted to explain alloaesthesia following cordotomy on the anatomical basis that an uncrossed ipsilateral spinothalamic tract exists in man. Mott (1892), who studied alloaesthesia in monkeys with hemispinal sections, explained the mechanism of alloaesthesia in the same way. We consider the mechanism of alloaesthesia in our patients both with spinal cord lesions and those with hypertensive cerebral haemorrhage in the same way as Ray and Wolff (1945). In our patients with right putaminal haemorrhage alloaesthesia occurred transiently in the acute stage, while brain oedema around the haemorrhage was present. It may therefore be better to consider that the dysfunction of the oedematous white matter surrounding the haematoma produces alloaesthesia than to consider that dysfunction of the putamen itself produces alloaesthesia. It is suggested that alloaesthesia in our patients caused not only by spinal cord lesions but also by hypertensive cerebral haemorrhage occurred when crossed sensory fibres were severely damaged on one side and consequently sensory inputs were conducted through the uncrossed fibres on the opposite side. Manifestations of higher cortical dysfunctions such as anosognosia may simply be incidental phenomena.

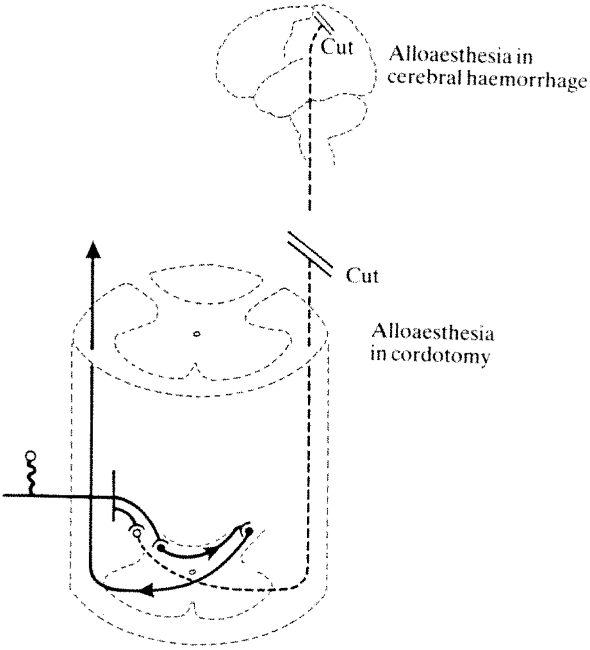
Cut
Alloaesthesia in cerebral haemorrhage
Cut
Alloaesthesia in cordotomy

FIG. 5. Speculative mechanism for alloaesthesia (redrawn from Ray and Wolff (1945)). For explanation *see* text.

Major questions still remain to be answered in relation to the mechanism of the ipsilateral disturbance in localizing the stimulated site in the recovery period and the rarity of alloaesthesia with thalamic haemorrhage.

ACKNOWLEDGEMENT

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ARHINENCEPHALY

THE SPECTRUM OF ASSOCIATED MALFORMATIONS

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SUMMARY

Eight cases are presented of arhinencephaly and its associated malformations, which included 2 examples of holoprosencephaly and 3 of agenesis of the corpus callosum. Additional features included cortical malformations, anomalies of the long tracts and of the optic pathway, cerebellar hypoplasia and dentato-olivary dysplasia. Each of these components covered a wide spectrum ranging in severity from extreme to minimal. Craniofacial dysmorphism, and cardiac, renal and endocrine disorders were present in some cases. Only 2 cases were associated with chromosomal abnormalities, 1 with trisomy 13, the other with partial trisomy 7(7q$^+$). Of possible environmental factors, maternal diabetes was recorded in 1 case. While all cases can be classified into broad categories, the individual variations render each case apparently unique.

INTRODUCTION

Kundrat (1882) applied the term ‘arhinencephaly’ to a group of cases which, apart from absence of the olfactory pathway, shared the feature of a single undivided forebrain. The term was found unsatisfactory by subsequent writers, as it emphasized a relatively minor, and perhaps inconstant, feature in a major developmental disorder. Alternative terms were proposed: holotelencephaly (Yakovlev, 1959), telencephalosynapsis (de Morsier, 1961), and holoprosencephaly (DeMyer and Zeman, 1963), the last of these being most widely accepted. Nevertheless, the term ‘arhinencephaly’ continued to be used as more or less synonymous with the others, and as an integral part of the cyclopia-ethmocephaly cebocephaly spectrum of malformations. Only recently a tendency has developed to use the term in its literal sense, meaning aplasia of the olfactory bulbs, tracts and tubercles irrespective of its associations (DeMyer, 1977; Jellinger *et al.*, 1981; Ludwin and Norman, 1985). The associations of arhinencephaly cover a wide range of developmental malformations both within and outside the central nervous system. While the literature on holoprosencephaly has been extensively reviewed (de Morsier, 1961; DeMyer, 1977; Probst, 1979), arhinencephaly without holoprosencephaly has been the subject of only a few studies (de

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Morsier, 1955; Dekaban, 1975). In an important statistical study of telencephalic malformations Jellinger *et al.* (1981) pointed out considerable differences in the associations of holoprosencephaly and 'pure' arhinencephaly, thus producing evidence that aplasia of the olfactory pathway may be a feature of more than one morphological entity. Valuable though such studies are, they cannot cover the finer points of structural aberrations, highlight unusual combinations of lesions, or correlate certain patterns with aetiological factors. These can be revealed only in detailed records of individual cases.

We have recently had the opportunity of studying the clinical and pathological features of 8 cases of arhinencephaly, some associated with holoprosencephaly, others with different malformations. Two of the patients died in the neonatal period, 2 in early infancy, 3 in childhood, and only 1 reached adult life. The patients with longer survival were all institutional inmates, severely mentally retarded and neurologically handicapped. The material is thus heavily biased towards multiple and extensive malformations and may not be representative of the full spectrum of arhinencephaly and its associated disorders.

CASE REPORTS

Case 1

Clinical Summary. V. was a 1.36 kg female infant born to a 31-year-old gravida 2, para 1, B Rh^+ mother after an uncomplicated pregnancy. Her gestational age was 35 wks by dates, 31 wks by examination. The infant was born by spontaneous vaginal delivery. Apgar scores at 1, 5 and 10 min were 1, 3 and 6, respectively. Initial examination was notable for microcephaly with midfacial hypoplasia. Growth parameters were: weight 1.36 kg, length 41 cm. occipitofrontal circumference (OFC) 23.5 cm. The anterior fontanelle was open and flat, 0.5 × 0.5 cm. There was hypotelorism and microphthalmia with corneal opacities. The nose had a flat bridge and a single nonpatent naris. There was micrognathia and microstomia with a poorly defined philtrum. The palate was high arched with three central ridges, but no cleft. The nipples were hypoplastic. Abdominal palpation disclosed two retroperitoneal masses, thought to be kidneys. The limbs were abnormal, shortened and rotated. The hands were maintained in ulnar deviation with flexion contractures of the second and third digits of each hand. A digital tag, lateral to the fifth digit, was present on the left. Neurological examination was not carried out and no neuroradiological studies were performed. Chromosome analysis of blood and skin revealed karyotype $47,XX,13^+$. The infant died at 9 h of age.

General autopsy findings. Multiple congenital anomalies: microcephaly, microphthalmia, midfacial hypoplasia with single naris, microstomia and micrognathia. Other anomalies: hirsutism, hypoplastic nipples, intrapancreatic ectopic spleen, polycystic kidneys (Potter type III). Pulmonary hyaline membrane disease.

Neuropathology (NP 28016). Gross appearances. The fixed brain weighed 80 g of which the cerebellum and brainstem accounted for 12 g. The undivided prosencephalon was horse-shoe shaped, the concavity being covered by a thin membrane. The convolutional pattern of the cortex consisted of a few broad gyri running horizontally across the midline. The floor of the common ventricle was formed by a median eminence representing the apparently fused basal ganglia and thalami. The brainstem was slender and the cerebellum small with an indistinct pattern of folia. The olfactory bulbs, tracts and tubercles were absent. The optic nerves were hypoplastic; other cranial nerves showed no gross abnormality.

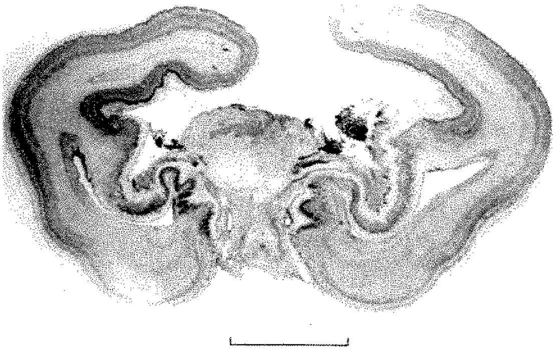

FIG. 1. *Case 1.* Coronal section of brain showing configuration of holoprosencephaly at thalamic level. Celloidin, Nissl stain. Bar = 1 cm.

Coronal sections through the forebrain confirmed the continuity of the poorly convoluted cortex across the midline, enclosing a common ventricle. The corpus callosum and septum pellucidum were absent. The basal ganglia and thalami were fused, there being no separate third ventricle. Transverse sections though the brainstem and cerebellum revealed absence of cerebral peduncles, a hypoplastic basis pontis and absent medullary pyramids.

Microscopy. The cerebral cortex varied in appearance in different areas. In some it showed the structure of a fairly well developed fetal cortex, with a smooth surface and good lamination, with a tendency to arrangement of the neurons in radial columns. In some areas there was a cell-free gap in the deeper layers, giving an appearance of a four-layered cortex. In some places this cell-free zone was broken up into islands. The surface of the cortex was irregular in many places, ranging from slight corrugation through a status verrucosus to a pattern resembling polymicrogyria. In one area on the medial surface the cortex was completely disorganized and formed a lattice of neurons with intervening cell-free spaces.

The thalami were fused in the midline and the individual nuclei were not identifiable. Near the midline the cytoarchitecture was completely disorganized, the neurons being arranged into irregular festoons. The well developed choroid plexuses of the lateral ventricles were situated near the lateral angles of the common ventricle, those of the third ventricle close to the midline. The roof membrane of the common ventricle began at the tela choroidea of the lateral choroid plexuses, followed the medial cortical surface of the arms of the 'horse-shoe' and continued to form the disrupted cyst (fig. 1).

Sections through the brainstem confirmed the absence of long tracts. There was a mass of ectopic glia in the subarachnoid space corresponding in position to the interpeduncular fossa. The aqueduct was widely patent and the fourth ventricle normal in size and shape. The pontine tegmentum was normal; the basis pontis consisted almost entirely of densely packed neurons of the nuclei pontis. In the medulla the well convoluted inferior olives occupied a position close to the midline on the ventral surface. The cerebellum was hypoplastic with short primitive folia, but the internal structure of the cortex was appropriate to the gestational age. Large collections of matrix cells were present in and around the dentate nucleus.

Eye pathology. The left eye measured 12.0 × 11.0 × 12.0 mm. Microscopy showed a thin corneal epithelium, thin Bowman's and Descemet's membranes, and apparently normal corneal stroma. The iris was seen superiorly, largely missing inferiorly. The ciliary body was normal. The lens was cataractous with posterior morgagnian globules. There was a coloboma of the retina from the equator to the optic nerve on the same side as the iris coloboma. The retina was dysplastic and peripherally attached to the posterior lens capsule (fig. 2). There was a densely cellular, vascular tissue between the lens and the detached retina, composed of plump spindle cells consistent with primary vitreous, also containing dendritic melanocytes. The optic nerve was severely hypoplastic.

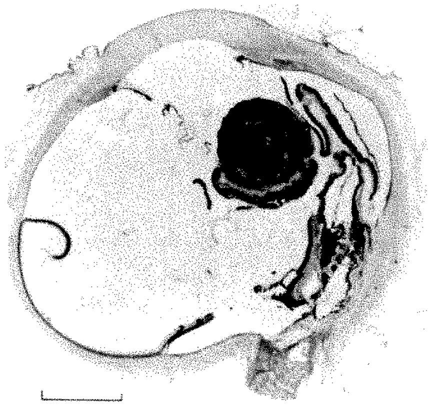

FIG. 2. *Case 1.* Eye showing partially detached dysplastic retina adherent to cataractous lens. Haematoxylin and eosin. Bar = 0.2 cm.

Case 2

Clinical summary. E.W., a female infant with normal 46 XX blood karyotype was delivered spontaneously to a 26-year-old primigravida mother after an uneventful full-term pregnancy. The parents were unrelated and there was no family history of congenital malformations.

The baby's Apgar scores were 6 and 7 at 1 and 5 min. She weighed 3.1 kg, measured 48.2 cm and had a head circumference of 29 cm. Multiple malformations included right microphthalmia, bilateral iris colobomas at 6 o'clock, right dacryostenosis, and right choanal stenosis. Her mouth was very small and the chin hypoplastic. A pilonidal dimple was present on the trunk and the limbs were normal. Skull X-rays demonstrated that the mandible was extremely small in the midline and was fused to the maxilla except in the region of the incisors where a circular opening remained. The temporomandibular joints were absent. Computed tomograms (CT) of the brain failed to demonstrate cerebral abnormalities. Radiographs of the spine revealed fused C2 and 3 vertebral arches and T1, 2 and 3 hemivertebrae. Oral examination after alveotomy performed at 4 months of age demonstrated no recognizable tongue or other structures. The nasopharynx contained a disarray of soft tissues with some remnants of hard palate.

The baby required a permanent tracheostomy and was first fed by a nasogastric, and later by a gastrostomy, tube. She was thought to be able to hear and see, but had a searching nystagmus. Spontaneous full range of movement of limbs was present, and all reflexes were intact. The infant, however, failed to thrive and did not achieve any developmental milestones. She died at the age of 2½ yrs.

General autopsy findings. The body weighed 5.9 kg, measured 66 cm in length, and had a head circumference of 33 cm. The internal organs were normal except for bronchopneumonia.

Neuropathology (*CA 84-4794*). Gross appearances. The brain weighed 294 g after fixation. The cerebellum and brainstem weighed 57 and 7 g, respectively. The brain was globular in shape due to the shortness of the frontal lobes which were fused along their entire ventral aspect and at the poles. There was a partial dorsal midline cleavage of the remainder of the frontal and the parietal lobes. The occipital lobes were completely separated.

The gyri were broad and tended to run in a fronto-occipital direction. The sylvian fissures were poorly formed. The temporal gyri were irregularly convoluted. The olfactory tracts and bulbs were missing. The optic nerves and chiasma were normal. The remainder of the cranial nerves, brainstem and cerebellum were normal.

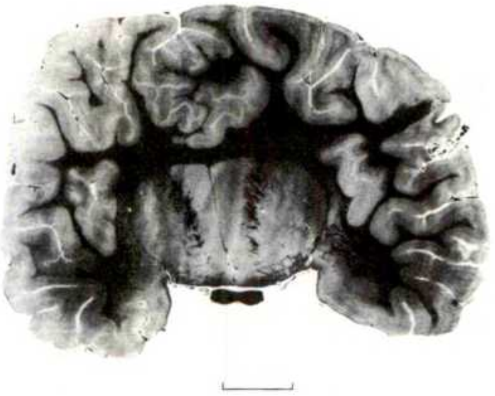

FIG. 3. *Case 2.* Coronal section of brain showing continuity of cortex across midline, fusion of caudate nuclei and obliteration of ventricle. Celloidin. Woelcke's myelin stain. Bar = 1 cm.

The blood vessels at the base of the brain were distributed in their usual pattern with the exception of the anterior cerebral arteries which were widely separated and coursed over the inferior surface of the frontal lobes. There was no anterior communicating artery.

Coronal sections of the cerebral hemispheres revealed that the interhemispheric dorsal fissure measured 2 cm in depth at its maximum. The cortical ribbon formed an intermingled mass deep in the midline and extended continuously across from one side to the other. At the site of the corpus callosum lay a thin band of white matter. The centrum semiovale was small. The frontal horns were obliterated anteriorly and represented by a linear seam. The heads of the caudate nuclei were rotated medially and fused in the midline. More posteriorly, the frontal horns became patent but were slit-like, forming a T-shaped cavity bordered by the caudate nuclei which were still closely approximated. The fornices and septum pellucidum could not be identified. A very small third ventricle was situated ventral to a large massa intermedia. The putamen, globus pallidus, mammillary bodies and lateral geniculate nuclei were normal in shape. The sylvian fissures were present, but the insulae were poorly developed. The hippocampal complexes were incompletely rotated. The fimbriae were present, but the crura were attenuated and disappeared into the most caudal portion of the transverse band of white matter bridging the cerebral hemispheres.

Microscopy. Small islands of heterotopic glial tissue were situated in the subarachnoid space. A typical polymicrogyric cortex covered the ventral surface of the frontal lobes and filled the depths of the partial dorsal cleavage between the cerebral hemispheres. The remainder of the cerebral cortex showed normal lamination.

The subcortical white matter contained small numbers of ectopic neurons. The centrum semiovale was small but well myelinated. The white matter band connecting both cerebral hemispheres was composed of three layers, a dorsal one of transverse fibres in the subcortical region, an intermediate one of fibres coursing in the fronto-occipital direction, and a ventral one consisting of transverse fibres separated from the ventricular lumen by a band of glial tissue covered by ependyma.

The completely obliterated tips of the frontal horns were recognizable by an ependymal seam. The heads of the caudate nuclei were rotated medially and fused in the midline, with the line of fusion demarcated by a line of ependymal cells (fig. 3). The basal forebrain nuclei were present. The septum pellucidum and fornices were absent. The mammillary bodies were well formed, and a mammillothalamic tract was identified. The massa intermedia was prominent and obliterated much of the third ventricle. The claustra could not be identified. The putamen, globus pallidus, thalamus, and lateral and medial geniculate bodies were normal on both sides.

The cerebral peduncles in the midbrain, the corticospinal and corticopontine tracts in the basis pontis, and the pyramids in the medulla were hypoplastic. The remainder of the internal structure of

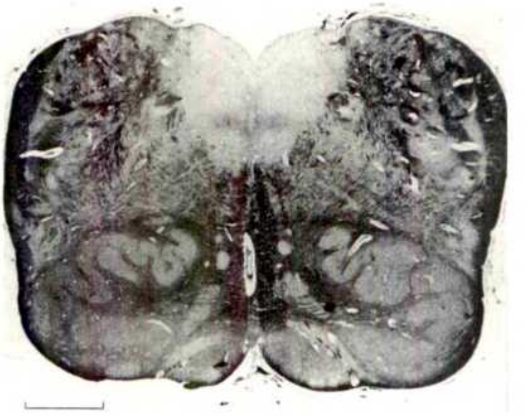

FIG. 4. *Case 2.* Medulla, showing abnormal configuration of inferior olives. Luxol fast blue-cresyl violet. Bar = 0.2 cm.

the midbrain, pons and medulla were normal except for minor dysplastic features of the inferior olives (fig. 4). These consisted of an horizontal arrangement, reduplication and fragmentation of the neuronal ribbon, and scattered ectopic neurons dislocated external to the nuclei bilaterally.

The dentate nuclei were unusually voluminous in the otherwise normal cerebellum.

Case 3

Clinical summary. N., a female infant, was the product of a full-term pregnancy of a 26-year-old gravida 6 para 5 mother with a history of insulin-dependent diabetes mellitus for six years. The mother gave a history of vaginal bleeding at 2 months and again at 6–7 months of her pregnancy. Spontaneous rupture of membranes occurred 8 h before delivery, preceded by a leak 2 days earlier. After vaginal delivery the infant's Apgar scores were 6 and 7 at 1 and 5 min respectively. She was floppy and apnoeic, and required immediate intubation.

On examination the striking feature was macrocephaly with an OFC of 40 cm. Other growth parameters were: weight 3.8 kg, length 56 cm, chest circumference 35 cm. The head was large with frontal prominence. The sutures were widely split, the width of the sagittal suture being 1.5 cm. The anterior fontanelle (5 × 7 cm) and the posterior (4 × 4 cm) were soft and slightly bulging. There was a suggestion of midfacial hypoplasia. The palpebral fissures were narrow. There was no coloboma or corneal clouding. A pug nose with a prominent bridge and normal nares were present. The palate was intact. The nipples were hypoplastic and widely spaced.

The pupils were equal and reacted sluggishly to light. Extraocular movements were dysconjugate with a tendency to left divergence. There were occasional periods of rapid random eye movements with 1–2 beats of nystagmus. Response to auditory stimulation was stronger on the right than on the left. The gag reflex was slightly depressed. The tongue exhibited occasional wiggling and rare sucking movements. Motor examination revealed decreased tone throughout. Spontaneous movements were present in all four limbs. Palmar and plantar grasp reflexes were present bilaterally. Tendon jerks were brisk. Withdrawal to painful stimuli was noted in all limbs.

Laboratory tests were unremarkable. The karyotype was normal 46 XX. A head CT scan showed a large midline cystic fluid collection communicating with the ventricles. The corpus callosum and septum pellucidum were absent. The findings were interpreted as consistent with lobar holoprosencephaly.

The infant died at 16 h of age.

General autopsy findings. Multiple congenital anomalies: macrocephaly, agenesis of pituitary, adrenal hypoplasia with loss of fetal cortex.

Neuropathology (*NP 27973*). Gross appearances. The fixed brain weighed 450 g, of which the cerebellum and brainstem accounted for 24 g. The cerebral hemispheres were separated by a deep cleft,

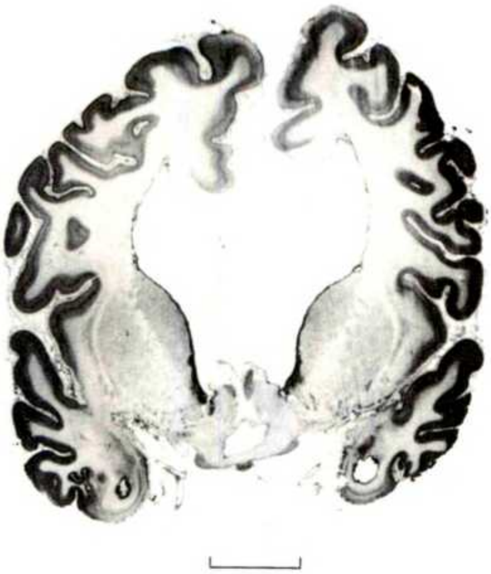

FIG. 5. *Case 3.* Coronal section of brain showing agenesis of corpus callosum and septum pellucidum. Celloidin, Nissl stain. Bar = 1 cm.

the cyst noted in situ having ruptured and collapsed. The convolutional pattern of the cerebral convexities was unremarkable. On the medial surface the cingulate gyrus was absent. The olfactory bulbs, tracts and tubercles were absent. The optic nerves were asymmetric, the right being smaller than the left. The lower cranial nerves appeared normal. There was a small rounded nodule of tissue in the position of the pituitary stalk. The mammillary bodies were widely separated by the stretched floor of the third ventricle. The brainstem and cerebellum were unremarkable.

Coronal sections confirmed the total absence of the corpus callosum and septum pellucidum. A prominent bundle of Probst was present on both sides. The fornix was lying free on the dorsal surface of the thalami which were not fused. The basal ganglia appeared normal. Transverse sections through the brainstem and sagittal sections through the cerebellum showed no significant abnormality.

Microscopy. The cerebral cortex and basal ganglia showed a normal neonatal structure. The roof of the interhemispheric cyst was formed by a glioependymal membrane attached to the margins of the bundles of Probst (fig. 5). The rudiment of the posterior pituitary showed the structure of a pituitary stalk. The optic tracts were thin, but symmetric and well myelinated.

The cerebellar cortex showed a normal neonatal structure. The dentate nucleus was abnormally large and excessively convoluted but showed normal cellular structure. There was a small cortical heterotopia, consisting of Purkinje and granule cells, in the white matter of the left cerebellar hemisphere. In the brainstem all major nuclei and fibre tracts were present, with myelination appropriate to the gestational age. The inferior olives appeared unduly compact, with the folds in close apposition and fused in places. The medullary pyramids were symmetric and well developed.

Case 4

Clinical summary. L.M. was a 9-week-old infant girl. She was born after a 36–37 week gestation to a healthy mother. The pregnancy was uncomplicated except for maternal oral herpes infection. Membranes has been ruptured 24 h before a spontaneous vaginal delivery. The child's birth weight was 2.78 kg, head circumference 30.5 cm. Apgar scores were 6 and 8 at 1 and 5 min respectively. At 9 wks of age she developed a fever of 40° C, was unresponsive and in status epilepticus. The CSF contained 4 white cells and 210 red cells/mm^3, glucose 4.3 mmol/l and protein 0.76 g/l. No organisms were seen.

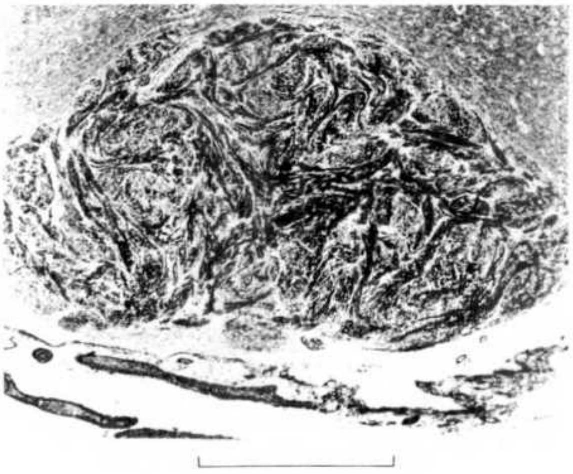

FIG. 6. *Case 4*. Midbrain, showing convoluted skein of nerve fibres in left cerebral peduncle. Bielschowsky's silver impregnation. Bar = 0.1 cm.

A CT scan showed enlarged ventricles and an absent corpus callosum. Treatment was started with antibiotics and anticonvulsants. This was followed by a respiratory arrest which responded to mechanical ventilation. At the same time increasing abdominal distension was noted. X-ray showed distended loops of large bowel compressing the diaphragm. The peritoneal fluid contained a few polymorphonuclear leucocytes and gram-negative rods. Culture eventually grew Enterobacteriaceae and Klebsiella pneumoniae. An exploratory laparotomy revealed visceral ischaemia and perforation of the distal ileum. During the operation the patient suffered a cardiac arrest and died at the age of 9 weeks.

General autopsy findings. Necrotizing gastroenterocolitis. Perforation of distal ileum. Peritonitis. Congestion of abdominal viscera. Septic spleen. Bilateral organizing bronchopneumonia.

Neuropathology (*NP 28117*). Gross appearances. The fixed brain weighed 340 g, of which the cerebellum and brainstem accounted for 32 g. The convolutional pattern was within normal limits except for the right temporal pole which showed a pattern of small irregular nodular gyri. The corpus callosum was absent and there was no identifiable cingulate gyrus. The olfactory bulbs, tracts and tubercles were absent, and the optic nerves and chiasma were small; the remaining cranial nerves appeared normal. Coronal sections confirmed total agenesis of the corpus callosum. The septum pellucidum was present, but its leaflets were widely separated and extended from the bundle of Probst to the fornix. The ventricles were enlarged at the expense of the considerably reduced white matter. Transverse sections through the brainstem revealed small cerebral peduncles and indistinct medullary pyramids. The cerebellum showed a deep interhemispheric cleft. Sagittal sections revealed a hypoplastic vermis and normal lateral lobes.

Microscopy. Apart from focal polymicrogyria at the right temporal pole, the cortical cytoarchitecture appeared normal. The white matter was considerably reduced in thickness; myelination was appropriate for age. The corpus callosum was absent and represented by bundles of Probst. The septum pellucidum joined the bundle with the fornix. No significant abnormalities were present in the basal ganglia or thalamus. The tectum and tegmentum of the midbrain were normal. The cerebral peduncles were hypoplastic and asymmetric, more fibres being present on the right. The distribution of the fibres was irregular, some running in the long axis of the brainstem, others intersecting them at various angles. In the left peduncle the fibres ended in a convoluted skein near the junction of the midbrain with the pons (fig. 6). The basis pontis consisted largely of the nuclei pontis with sparse and irregularly distributed transverse fibres. A small descending tract was present only on the right. In the medulla the inferior olives were abnormally convoluted. No pyramid was present on the left; on the

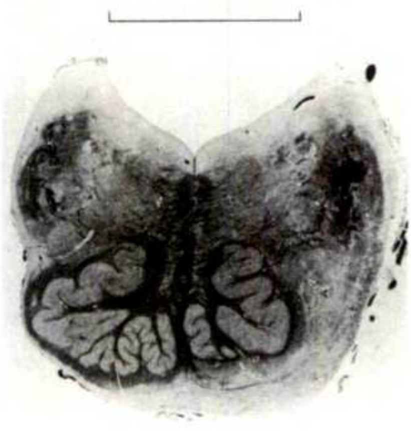

FIG. 7. *Case 4.* Medulla, showing asymmetry and abnormal configuration of inferior olives, absence of left pyramid and rudimentary right pyramid. Luxol fast blue-cresyl violet. Bar = 0.5 cm.

right it was represented by a thin crescent of fibres lying ventral to the olive (fig. 7). The arcuate nuclei were fused in the midline. There was dense fibrillary gliosis throughout the brainstem.

The cerebellar vermis consisted of only a few well developed, somewhat elongated, folia. The internal structure of the cortex was normal, as it was also in the cerebellar hemispheres. The dentate nuclei were large, irregularly convoluted and broken up into islands separated by strands of lightly myelinated fibres.

Case 5

Clinical summary. B.W., male, aged 9½ yrs at death. His family history and that of the pregnancy and birth are unknown. Multiple congenital abnormalities were noticed at birth: an asymmetric skull, more prominent on the right, an occipital encephalocele, hypertelorism with slanting palpebral fissures, a depressed bridge of the nose, a right harelip extending into the right nostril, a cleft palate, and cryptorchidism. In view of a leak from the encephalocele sac it was excised immediately after birth and found not to contain any neural tissue. An air ventriculogram carried out at the age of 12 days showed asymmetry of the cerebral hemispheres with a 7 mm right to left shift of midline structures. There was no septum pellucidum. The left lateral ventricle showed a dilated rounded anterior horn. The right ventricle was distorted by what appeared to be soft tissue masses arising from the ventricular wall. The third ventricle was partly occluded by a large massa intermedia, but communicated freely with the suprachiasmatic recess. Chromosomal analysis revealed a normal karyotype.

The child never achieved any developmental milestones, acquired no voluntary movements and remained severely mentally retarded with an untestable IQ. At the age of 1 yr his harelip was repaired surgically. He had severe feeding problems and was fed by nasogastric tube. He suffered from frequent seizures, inadequately controlled with large doses of anticonvulsants. An EEG carried out a year before death showed a slow medium voltage background activity with paroxysmal bursts of high voltage sharp waves.

His hospital course was punctuated by numerous respiratory infections. At the age of 9½ yrs he suffered a cardiorespiratory arrest and did not respond to resuscitative measures.

General autopsy findings. Pulmonary oedema. Cryptorchidism. Craniofacial dysplasia with cleft palate and repaired harelip. Repaired occipital encephalocele.

Neuropathology (C-009-85). Gross appearances. The fixed brain weighed 1000 g, of which the cerebellum and brainstem accounted for 73 g. The brain was asymmetric, the right hemisphere being larger than the left. A part of the right inferior temporo-occipital cortex was herniated into the posterior fossa and separated from the remainder of the hemisphere by a deep tentorial indentation.

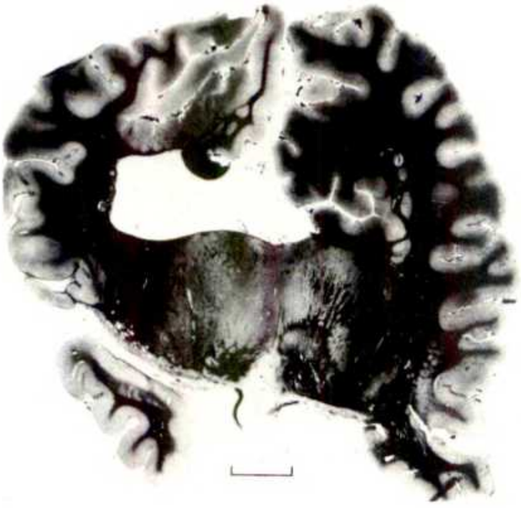

FIG. 8. *Case 5*. Coronal section of brain showing abnormal configuration of cortex, subcortical heterotopias and fusion of basal ganglia. Celloidin, Woelcke's myelin stain. Bar = 1 cm.

The herniated cortex lay in close apposition to an apparently single cerebellar hemisphere with which it shared a common leptomeningeal covering. The convolutional pattern of the cortex was strikingly abnormal throughout. The cortex was thrown into small folds, intersected by deep sulci, running more or less vertically. The olfactory bulbs, tracts and tubercles were absent. The optic nerves and chiasma were thin. After separation of the brainstem it became apparent that the cerebellum consisted almost entirely of the right hemisphere. The vermis was absent and replaced by a cyst, the wall of which lay in close apposition to the cerebellar hemisphere.

Coronal sections revealed a grossly abnormal ventricular system. The corpus callosum and septum pellucidum were absent. A bundle of Probst was present only on the left. On the right an irregularly convoluted cortex formed the medial aspect of the hemisphere and extended to the lateral margin of the caudate nucleus. The basal ganglia and thalami were fused in the midline, reducing the third ventricle to a narrow ventral channel, communicating anteriorly with a large supraoptic recess, posteriorly with the common lateral ventricle. The aqueduct was widely patent. The fourth ventricle was continuous with the cyst replacing the vermis. The brainstem was slender and asymmetric, the right half being larger than the left.

Microscopy. In most areas the cerebral cortex showed normal lamination. A few gyri showed abnormal myelination of the molecular layer, the myelinated fibres running roughly parallel to the pial surface. Foci of polymicrogyria were seen, particularly in the left hemisphere. Several cortical heterotopias were present in the well myelinated white matter. The basal ganglia and thalami were malrotated and asymmetrically fused in the midline (fig. 8). The optic chiasma was thin and displaced laterally by a dilated supraoptic recess.

The right cerebellar hemisphere showed normal structure of the folia. The dentate nucleus was broken up into numerous islands, separated by strands of white matter. The vermis was absent and replaced by a glioependymal roof membrane, continuous with the fourth ventricle. Near its point of origin it contained a few rudimentary folia. It lay in close apposition to the medial surface of the right cerebellar hemisphere. On the left it was attached to a rudimentary left hemisphere, consisting of two folia on the lateral surface and a dysplastic cortical nodule medially (fig. 9).

The brainstem was asymmetric. The left superior cerebellar peduncle was absent, the left middle and inferior peduncles rudimentary. The left pyramidal tract was absent, the left medial lemniscus smaller than the right. The left basis pontis contained numerous neurons of the nuclei pontis and sparse transverse fibres, the right scanty neurons scattered among crowded transverse fibres. Both inferior

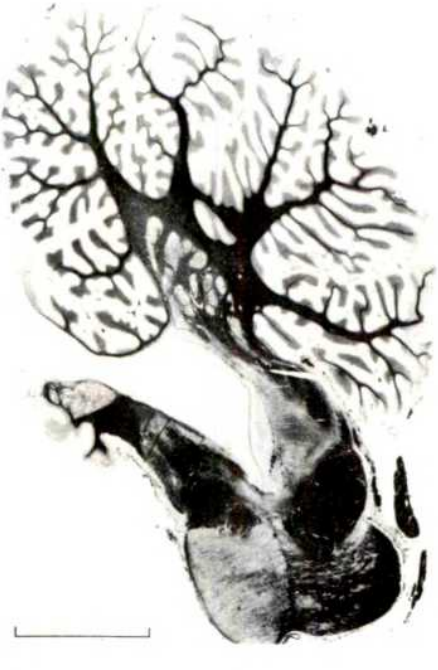

FIG. 9. *Case 5*. Pons and cerebellum, showing agenesis of vermis, rudimentary left cerebellar hemisphere, dysplastic right dentate nucleus and asymmetry of pons. Luxol fast blue-cresyl violet. Bar = 1 cm.

olives were primitive in configuration, C-shaped and devoid of folds (fig. 10). The left was larger than the right, the latter being sparsely cellular. Both dorsal accessory olives were absent, the medial ones rudimentary.

Case 6

Clinical summary. J.C., a male, aged 21 yrs at death, was the product of a normal pregnancy and birth. Five other siblings were healthy. The patient was noted to be abnormal from birth, but no details of the early history are available before the age of 2½ yrs. At that time he was found to be severely mentally retarded, with an IQ of 6. He had no speech, no voluntary movements and no sphincter control. He had a large and almost completely bald head, but no dysmorphic facial features apart from a high arched palate. He was blind with bilateral optic atrophy, but apparently not deaf. He was quadriplegic with spasticity, flexion contractures and kyphoscoliosis. His major underlying medical

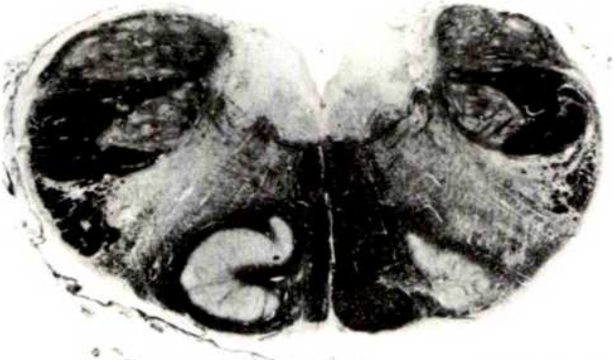

FIG. 10. *Case 5*. Medulla, showing primitive, dysplastic and asymmetric inferior olives. Luxol fast blue-cresyl violet. Bar = 0.2 cm.

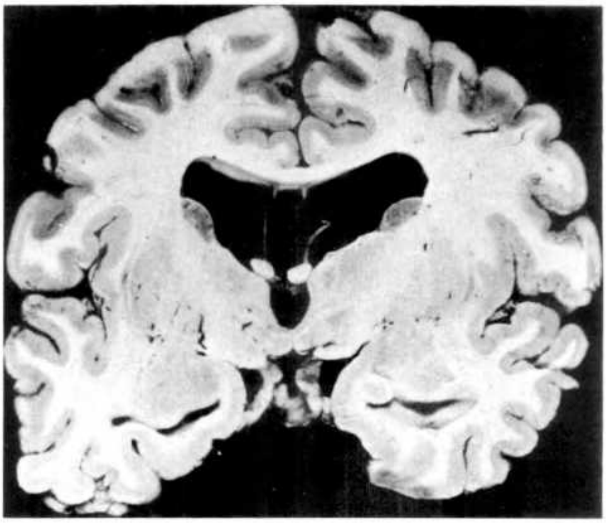

FIG. 11. *Case 6*. Coronal slice of brain showing rudimentary thread-like septum pellucidum.

problem was congenital heart disease, diagnosed as ventricular septal defect and pulmonary stenosis. Laboratory investigations were within normal limits except for mild polycythaemia (Hb 15.6 g). Chromosomal analysis revealed a normal karyotype (46 XY).

During his stay in hospital he had repeated major seizures, apparently well controlled with phenobarbital. His course was punctuated by repeated respiratory infections and episodes of contact dermatitis. At the age of 21 he was found apnoeic and could not be resuscitated.

General autopsy findings. Tetralogy of Fallot. Polycythaemia. Hydronephrosis of left kidney with stenosis of pelviureteric junction. Total alopecia.

Neuropathology (*C-007-85*). Gross appearances. The fixed brain weighed 1600 g of which the cerebellum and brainstem accounted for 150 g. The convolutional pattern was abnormal with sulci running radially towards the sagittal fissure. The gyri were broad in the anterior part of the brain, small and excessively convoluted posteriorly. On the orbital surface the gyri recti were short and present only in the posterior half. There was no clear division into orbital gyri. The olfactory bulbs, tracts and tubercles were absent. The optic nerves were thin; the lower cranial nerves appeared normal.

Coronal sections showed an apparently normal cortical ribbon with a downward displacement of the area striata which extended well onto the inferior surface of both occipital lobes. The lateral ventricles were enlarged and joined anteriorly through a large defect in a rudimentary septum pellucidum, which was represented by two thin, string-like, structures running from the corpus callosum to the roof of the third ventricle (fig. 11). The left septal rudiment was represented anteriorly by a thin ridge on the inferior surface of the otherwise normal corpus callosum. The basal ganglia, thalami, brainstem and cerebellum were unremarkable.

Microscopy. The cerebral cortex was well laminated and normally myelinated. Numerous scattered ectopic neurons were present in the underlying well-myelinated white matter. The corpus callosum was normal. The ridge representing the left leaf of the rudimentary septum pellucidum contained a few myelinated fibres. The basal ganglia and thalamus showed a normal neuronal population. Scattered calcospherites, in places grouped around blood vessels, were seen in the globus pallidus, putamen, thalamus and internal capsule. The optic nerves were thin and flattened, with crowded septa and thin, finely vacuolated fascicles of myelinated fibres.

The cerebellar cortex was normal. The dentate nuclei were excessively convoluted, partially broken up and contained a few ectopic neurons scattered in the adjacent white matter. The major nuclei of the midbrain and pons appeared normal. The cerebral peduncles were of normal size, but showed some pallor of myelin in their central portions, as also did the long tracts in the basis pontis. The inferior olives were normally convoluted, but several neurons were displaced into the white matter both of the fleece and the hilum. The dorsal accessory olive was excessively convoluted and resembled the principal olivary nucleus in its structure.

Case 7

Clinical summary. D.S., a male, aged 16 months at death, was born by spontaneous vaginal delivery after a normal 40 wk gestation. His birth weight was 2570 g, Apgar scores 4 and 7 at 1 and 5 min, respectively. Multiple congenital anomalies were noted at birth: simian creases, rocker bottom feet, low set ears and excessive skin folds in neck. A chromosomal analysis revealed a partial trisomy 7. He had no response to visual or auditory stimuli, remained respirator dependent and required a tracheostomy and gastrostomy.

At the age of 6 months his developmental level was below that of 1 month. His head circumference was 42 cm and his anterior fontanelle was wide open. His face was dysmorphic and asymmetric, with hypertelorism, low set ears and a high arched palate. His rocker bottom feet had short big toes and long second and third toes. His limbs were hypotonic, with fair strength and poor coordination. His tendon reflexes were brisk and superficial reflexes intact. He responded to pain, touch and pressure.

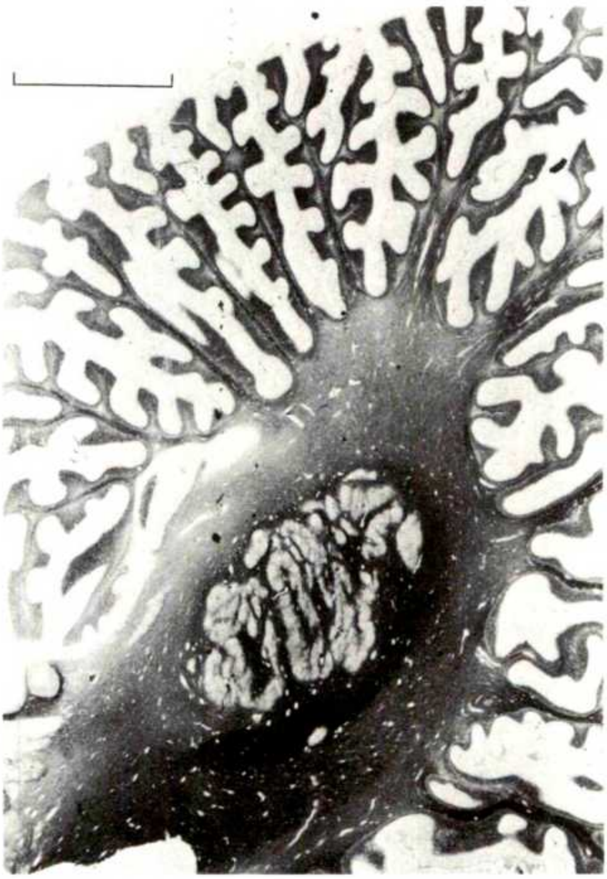

FIG. 12. *Case 7*. Cerebellum, showing dysplastic broken up dentate nucleus. Luxol fast blue-cresyl violet. Bar = 0.5 cm.

Laboratory findings were unremarkable. Major motor seizures were controlled with phenobarbital. Recurrent respiratory infections, and infections of the tracheostomy and gastrostomy stomas responded to appropriate antibiotic treatment. He suffered a cardiorespiratory arrest after inhalation of vomit following a gastrostomy feed. Resuscitation was unsuccessful.

General autopsy findings. Pulmonary oedema. Splenomegaly. Tracheostomy and gastrostomy.

Neuropathology (*C-015-85*). Gross appearances. The fixed brain weighed 750 g, of which the cerebellum and brainstem accounted for 58 g. The convolutional pattern was irregular with no distinct separation of the frontal or temporal gyri. The sylvian fissure was shallow and ran vertically. The gyral pattern of the orbital surface was disorganized. The olfactory bulbs, tracts and tubercles were absent. The optic nerves were smaller than normal. The cerebellum was small and did not reach the occipital pole. Coronal sections showed an apparently normal cortical ribbon, reduced bulk of the white matter and symmetric, moderately dilated lateral ventricles. The corpus callosum was thin, particularly in its posterior part. The septum pellucidum was present. The basal ganglia and thalami appeared normal. The brainstem was slender and the cerebellum somewhat smaller than normal, but both showed normal configuration.

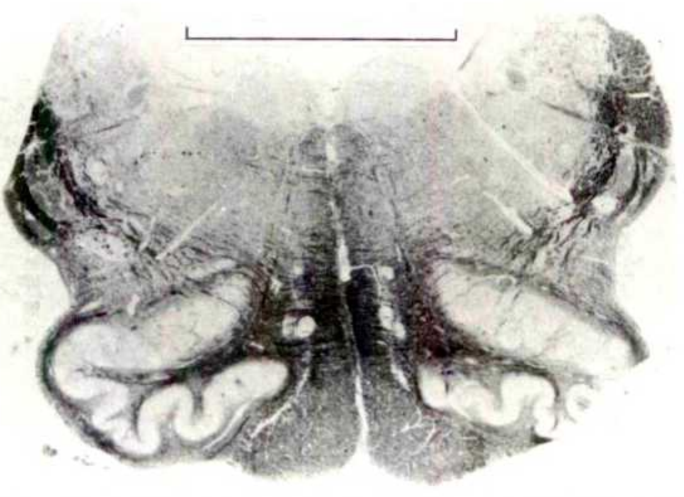

FIG. 13. *Case 7*. Medulla, showing dysplastic dorsal folium of both inferior olives. Luxol fast blue-cresyl violet. Bar = 0.5 cm.

Microscopy. The lamination and orientation of cortical neurons appeared normal, but numerous ectopic neurons were scattered in the subcortical white matter. Myelination was appropriate for the patient's age. The basal ganglia and the thalami were normal. The optic nerves were thinner than normal and somewhat flattened, with slender but well myelinated fibre bundles separated by crowded collagenous septa. The cerebellar cortex showed normal structure. The dentate nucleus was abnormally convoluted and broken up into isolated islands (fig. 12). There was dense fibrillary gliosis of the cerebellar white matter. Widespread gliosis was also present in the brainstem, around the aqueduct, in the floor of the fourth ventricle, in the red nuclei, the superior cerebellar peduncles, the raphe and the central reticular substance. The aqueduct was forked with the ventral lumen obliterated and surrounded by ependymal rosettes. The inferior olives were dysplastic, with the ventral folium showing a few simple convolutions, while the dorsal folium was broad and straight (fig. 13). The medial accessory olives were broken up into small circular islands. The dorsal accessory olives were hypoplastic.

Case 8

Clinical summary. A.T., a girl, was born to a 31-year-old gravida 2, para 1, ORh-ve mother after an uncomplicated full-term pregnancy. There was a history of possible cocaine abuse during the first trimester. The infant was delivered vaginally after pitocin augmentation and artificial rupture of membranes. Birth weight was 3.33 kg, Apgar score 5 and 8 at 1 and 5 min, respectively. Multiple congenital anomalies were noted.

The skull was tower-shaped and asymmetric, the right frontal area being broad and flat compared with the left. The anterior fontanelle was closed and represented by a small depression, 1 × 1 cm. The right orbit was hypoplastic and the palpebral fissure down-slanting. Ophthalmological examination revealed a coloboma of the left iris, lens, choroid, retina, and optic nerve, and a coloboma of the right retina. The nasal bridge was broad with a long flat nose; the nares were patent. The right ear was low and posteriorly rotated. Both ears had folded hypoplastic helices and absent lobules. The palate was high arched. A holosystolic cardiac murmur was present. Cardiac catheterization revealed mitral and pulmonary atresia, a hypoplastic left ventricle, an overriding aorta arising almost exclusively from the right ventricle, and a right-sided aortic arch.

Neurological examination revealed mildly increased tone, particularly in the lower extremities, no spontaneous purposeful movements and no consistent response to environmental stimuli. The karyotype was normal (46 XX). An EEG showed general slowing with multifocal sharp waves.

The infant underwent a modified Blalock-Taussig shunt operation on the fifth day. Her condition, however, failed to improve, she went into increasing cardiac failure with progressive anasarca, failing cardiac output and deteriorating respiratory function. Persistent seizures failed to respond to treatment on the seventeenth day.

General autopsy findings. Congenital heart defects with mitral and pulmonary atresia, hypoplastic left ventricle, atrial and ventricular septal defects, closed ductus arteriosus and right-sided aortic arch. Modified Blalock-Taussig shunt between anomalous left subclavian artery and left pulmonary artery. Hepatic congestion with centrilobular necrosis. Multiple craniofacial anomalies.

Neuropathology (*NP 28 100*). Gross appearances. The fixed brain weighed 400 g, of which the cerebellum and brainstem accounted for 25 g. The convolutional pattern of the cerebral hemispheres was normal. Except for absence of the olfactory bulbs, tracts and tubercles the cranial nerves appeared normal. There was extensive infarction of the left frontal cortex in the watershed zone, a more limited area of softening in the right frontal lobe, and massive softening of the right temporal and occipital lobes. The corpus callosum and septum pellucidum were present. The cerebellum appeared flattened with short, poorly developed folia, particularly on the superior surfaces. The brainstem appeared within normal limits.

Microscopy. Except for extensive anoxic and ischaemic lesions no significant abnormalities were found in the cerebral hemispheres. The cerebellar folia were generally hypoplastic, short and poorly branched, but showed normal infantile structure of the cortex. The dentate nucleus showed minor abnormalities of its configuration with splitting in places. There were massive neuronal heterotopias consisting predominantly of large cells in the white matter of both cerebellar hemispheres. The brainstem showed no major structural abnormality except for some dysplasia of the inferior olives. The left olive was normally convoluted, but malrotated, the hilum pointing dorsally, the right was arranged in parallel lamellae. More caudally a more normal pattern was seen with a somewhat hypoplastic ventral folium. Superimposed on these abnormalities were anoxic changes with patchy neuronal loss and neurons undergoing acute necrosis throughout the brainstem.

DISCUSSION

Clinical Features

The material presented here is highly selective and heavily biased towards severe disabilities, either incompatible with life or requiring life-long institutional care.

It is therefore not surprising that all patients who survived beyond the neonatal period were severely mentally retarded, never developed normal milestones and had intelligence quotients at the lowest end of the scale. Most of them had severe motor disabilities, ranging from total lack of spontaneous movements to a spastic quadriparesis. None of them had sphincter control. Severe feeding difficulties required feeding by nasogastric tube or gastrostomy. With the exception of Case 2 all survivors suffered from seizures.

A few points require further comment. Facial dysmorphism is a common, but not constant, feature of arhinencephaly (DeMyer *et al.*, 1964; DeMyer, 1975). The classical midfacial hypoplasia, due to maldevelopment of the parts derived from the frontonasal process, is a feature of holoprosencephaly rather than of arhinencephaly per se. The syndrome consists of hypotelorism which may range from a slight reduction of the interpupillary and intercanthal distance to a single midline eye. The nasal malformations range from a flat nose with a single, often blind, nostril (cebocephaly) to a proboscis situated between the eyes (ethmocephaly) or above the single eye (cyclopia). Abnormalities of the upper lip include an absent or indistinct philtrum or a midline defect. The intermaxillary bone may be absent and the palate either cleft or high arched. These features at the cebocephalic end of the spectrum are well illustrated by our Case 1.

Case 2 presented an unusual complex of dysmorphic features, already briefly reported by Dobrow (1983). The parts affected were predominantly those derived from the branchial arches, and not from the frontonasal process. The mandible was hypoplastic and fused with the maxilla with the exception of a circular opening situated anteriorly. The temporomandibular joints were absent. The mouth was small and circular, the tongue and palate rudimentary. Syngnathia is a rare malformation which may appear in different contexts. Wehinger (1970) reported a case associated with peromelia but no indication of a neurological disorder. The association of syngnathia with holoprosencephaly in our Case 2 appears to be exceptional, perhaps even unique.

Cases 3, 4 and 6 displayed no significant dysmorphic features. Case 5 showed a craniofacial asymmetry with an occipital encephalocele, hypertelorism, a depressed nasal bridge, a right lateral harelip and a cleft palate. Hypertelorism, facial asymmetry, low set ears and a high arched palate were present in Case 7. Asymmetry of the skull, hypoplasia of the right orbit, a long flat nose and a high arched palate were features of Case 8.

Ocular abnormalities are common in the arhinencephalic syndromes (Karseras and Lawrence, 1975). They range from anophthalmia through microphthalmia to a variety of colobomas. Bilateral microphthalmia was present in our Case 1, unilateral in Case 2. Multiple colobomas were seen in Cases 1, 2 and 8.

Pathology: Central Nervous System

Arhinencephaly. The term is used here in the strict sense of aplasia of the olfactory bulbs, tracts and tubercles irrespective of its associations.

General configuration of the brain. The size of the brains ranged from extreme micrencephaly (80 g in a neonate, Case 1; 294 g in a 2½-yr-old child, Case 2) to abnormally large ones (450 g in a neonate, Case 3; 1600 g in an adult, Case 6). Apart from holoprosencephaly, which is discussed below, the convolutional pattern was more or less abnormal in all cases. The abnormality was most severe in Case 5 in which no normal gyri could be identified, deep sulci running more or less vertically over the convexity. In most cases abnormalities of gyral pattern could be seen on the orbital surface of the frontal lobes: short or poorly developed gyri recti and indistinct separation of the orbital gyri. The pattern of the medial surface depended on the presence or absence of the corpus callosum. In the latter situation the cingulate gyrus was absent and radial sulci ran to the edge of the cortex. Here again the pattern in Case 5 was most abnormal, the cortex on the medial surface of the right hemisphere extending to the lateral margin of the caudate nucleus.

Holoprosencephaly. The term implies a whole or undivided forebrain. It includes a wide spectrum ranging from a complete failure of differentiation of the telencephalic vesicles to a partial fusion of otherwise well developed hemispheres. A widely accepted classification is that of DeMyer and Zeman (1963) who divided the holoprosencephalies into alobar, semilobar and lobar. The alobar ones have a small monoventricular cerebrum undivided into lobes or hemispheres. The roof of the single ventricle is constituted by a thin membrane which may form a cyst. Our Case 1 is an example of this group. In the semilobar type an incomplete interhemispheric fissure is present, at least posteriorly. The cerebral neocortex is in broad continuity across the midline anteriorly while posteriorly the occipital lobes show an approximately normal configuration. Our Case 2 conforms to this pattern. Lobar holoprosencephaly has been subdivided into two types: in one the hemispheres are well developed but joined by a continuous band of neocortex at the frontal pole, the orbital surface or over the corpus callosum. This last variant (the 'cingulosynapsis' of Constantinidis, 1969) forms the mildest type of holoprosencephaly. The second type of lobar holoprosencephaly shows complete separation of the neocortex across the midline, usually with an absent or hypoplastic corpus callosum. It is this group, represented by our Case 3, which has led to greatest terminological difficulties. From a strictly morphological point of view a holoprosencephaly with complete separation of the hemispheres is a contradiction in terms. Attempts to define this group have often relied on criteria of doubtful validity. Osaka and Matsumoto (1978) postulate agenesis of the corpus callosum and of the falx as absolute criteria of any form of true holoprosencephaly, but both are inconstant and nonspecific features. Both de Morsier (1954, 1961) and Probst (1979) clearly distinguish the cortical fusions from commissural defects. It thus appears desirable to confine the term 'holoprosencephaly' to malformations with a midline continuity of the neocortex. This plea for terminological accuracy does not prejudge the validity of the hypothesis that all telencephalic midline defects share common pathogenetic mechanisms (Loeser and Alvord, 1968; Jellinger and Gross, 1973; Jellinger *et al.*, 1981).

Commissural defects. Agenesis of the commissural system is a constant feature of alobar holoprosencephaly. In semilobar holoprosencephaly the corpus callosum may be present and it appeared to be present in our Case 2. It is, however, doubtful if the entire band of white matter joining the two hemispheres represented commissural fibres. It consisted of three layers: tangential fibres parallel to the cortex and probably representing the subcortical U-fibres, a bundle of longitudinal fibres and a thin layer of transverse fibres adjacent to the subependymal glia, this last group possibly representing true commissural fibres. Agenesis of the corpus callosum independent of holoprosencephaly was seen in Cases 3, 4 and 5. As mentioned above, we prefer to interpret Case 3 as 'agenesis of corpus callosum with diencephalic cyst' (Brockelhurst, 1973) or 'with interhemispheric cyst' (Probst, 1973) rather than as 'lobar holoprosencephaly'. In all 3 cases a longitudinal bundle of Probst replaced the corpus callosum. In Cases 3 and 4 it was present bilaterally, in Case 5 only on the left. Case 4 differed from Case 3 only in the fact that a septum pellucidum was present, its widely separated lamellae extending from the bundle of Probst to the fornix (Loeser and Alvord, 1968). The septum pellucidum was absent in Cases 2, 3 and 5 and rudimentary in Case 6.

The cerebral cortex. No attempts were made to study the cortical cytoarchitecture in detail. Little can be added to Yakovlev's (1959) definitive study of the cortex in alobar holoprosencephaly from which it appeared that in some cases all major cytoarchitectural areas could be identified, while in others the cortex was severely disorganized. Our Case 1 belongs to the latter group, corresponding to Yakovlev's Cases 3 and 6, in which the cortex showed abnormal lamination with areas of status verrucosus deformans and of frank polymicrogyria. Polymicrogyria was present focally in a few other cases: on the ventral surface of the frontal lobes and in the interhemispheric fissure in Case 2, in the right temporal pole in Case 4 and in the left hemisphere is Case 5. Grey matter heterotopias were prominent in Case 5. Scattered ectopic neurons in the white matter were frequently seen. While this is a finding of doubtful significance in neonates, it was also present in older patients (Cases 2, 6 and 7) in whom it may represent a minor disorder of migration.

The basal ganglia. Fusion of the basal ganglia or thalami is a common finding in all variants of holoprosencephaly but is not confined to this group of malformations. Both the basal ganglia and the thalami were fused in Case 1. In Case 2 the heads of the caudate nuclei were fused in the midline and with the ventricular roof, thus obliterating completely the anterior end of the common ventricle, and the thalami were joined by a large massa intermedia. A similar configuration of the basal ganglia was illustrated by Probst (1979) in a case classified as 'prosencephaly intermediate type A' (equivalent to semilobar holoprosencephaly). An asymmetric fusion was present in Case 5.

The pyramidal tracts. Pyramidal tracts are usually absent in alobar holoprosencephaly and were not seen in Case 1. In Case 2 the medullary pyramids were present, but were hypoplastic and poorly myelinated. Severe hypoplasia of pyramidal tracts was seen in Case 4, where the left pyramid was totally absent and the right represented by a thin crescentic bundle of fibres sandwiched between the inferior olive and a large arcuate nucleus which bridged the midline. Even more remarkable was the configuration of the long tracts in the cerebral peduncles which consisted of interwoven skeins of myelinated fibres, resembling a traumatic neuroma. Absence of the left pyramidal tract was also noted in Case 5. No long tract abnormalities were seen in cases with a normal corpus callosum. The frequent association of anomalies of the pyramidal tracts with agenesis of the corpus callosum was noted by Parrish *et al.* (1979). In most of their cases the aberrations from the normal pattern were slight and consisted of asymmetry, faulty decussation or abnormal distribution of the tracts in the spinal cord. Total absence of pyramidal tracts in callosal agenesis appears to be extremely rare.

The optic pathway. Regrettably an eye has been examined only in Case 1 and showed the well known malformations associated with trisomy 13 (Hoepner and Yanoff, 1972; Howard, 1981). These included microphthalmia, colobomas of the iris and retina, cataract, retinal detachment and dysplasia, and a persistent primitive vitreous. Colobomas were also observed clinically in Cases 2 and 8, as noted above. Some degree of hypoplasia of the optic nerves was seen in most cases, with the possible exception of Cases 2 and 8.

Cerebellar hypoplasia. Small cerebella with short, stunted, simplified folia, but with normal cortical architecture, were seen in Cases 1 and 8. Hypoplasia of the vermis, which consisted only of a few folia, was a feature of Case 4. Total agenesis of the vermis, associated with a rudimentary and dysplastic left cerebellar hemisphere was present in Case 5. In this case, however, this abnormality may have been linked with the occipital encephalocele, a condition in which agenesis of the vermis is a common feature (Karch and Urich, 1972; Padget and Lindenberg, 1972; Caviness and Evrard, 1975; Friede, 1978). There are, however, several reports in the older literature of agenesis of the vermis in holoprosencephaly both with and without occipital encephalocele (de Morsier, 1961).

Cerebellar heterotopias. Three types of heterotopia were seen in the present material: aggregation of matrix cells in and around the dentate nucleus (Case 1), large cell heterotopias in the white matter (Case 8) and focal aggregations of disorganized cortical cells ('heterotaxia') in the white matter of the cerebellar hemispheres (Case 3). The significance of these findings is difficult to assess, as all these ectopias can be found in normal infants (Rorke *et al.*, 1968). Massive accumulation of primitive matrix cells, resembling the cells of the external granular layer, is, however, a common feature of trisomy 13 (Norman, 1966; Terplan *et al.*, 1966) and is occasionally encountered in other trisomies.

Dentato-olivary dysplasia. Jellinger *et al.* (1981) emphasized the association of dentato-olivary dysplasia with 'pure' arrhinencephaly in contrast with holoprosencephaly in which this abnormality was never found in their material. The problem here is largely one of definition, as only arbitrary decisions can be made on which deviations from the normal pattern of the dentate and inferior olivary nuclei qualify for the term 'dentato-olivary dysplasia'. If the term includes only dentate nuclei consisting of isolated islands of cells without formation of the normal convoluted ribbon and of primitive olives, totally or partially devoid of convolutions, as seen in our Cases 5 and 7, then our findings agree with those of Jellinger *et al.* (1981). In none of our cases, however, were the dentate and olivary nuclei completely normal. Partial fragmentation or abnormal branching of the dentate ribbon was seen in most cases, as was fragmentation, crowding or stunting of the olivary convolutions. Another abnormal finding was the presence of ectopic neurons in the white matter of the fleece and the hilum of the dentate and olivary nuclei. In one case, moreover, a typical dysplastic dentate nucleus was found in association with relatively minor abnormalities in the olives (Case 4). Evidently the dentate and olivary nuclei may be subject to a wide spectrum of abnormalities, some of which are difficult to classify.

Pathology: Associated Lesions in Other Systems

In his analysis of recently reported cases of holoprosencephaly, DeMyer (1977) emphasized the fact that multisystem involvement is commonly associated with chromosomal abnormalities, while isolated cerebral malformations are seen in patients with normal karyotype, although he admitted exceptions to this rule. No similar study has been carried out on arhinencephalies unassociated with holoprosencephaly and the present material is too small to allow any valid conclusions.

Cardiovascular system. Two of our cases (Cases 6, 8) had major cardiac malformations, one a tetralogy of Fallot, the other pulmonary and mitral atresia with septal defects and an overriding aorta. Neither of these was associated with chromosomal abnormalities or with holoprosencephaly, in fact the most severe cardiac anomaly was associated with the least severely affected brain (Case 8).

Other visceral abnormalities. Polycystic kidneys (Potter type III) and splenic ectopia in the pancreas, both common findings in trisomy 13, were found in Case 1. No visceral lesions were found in Case 7 (partial trisomy 7).

Endocrine system. Information on the state of the pituitary was available only in Cases 1, 2, 3 and 8, and in 3 of these it appeared to be normal. No anterior pituitary tissue was found in Case 3, in which the adrenals were hypoplastic with an absent fetal layer, findings similar to those seen in anencephaly. Agenesis of the pituitary with endocrine hypoplasia has been observed in rare cases of holoprosencephaly (Edmonds, 1950; Haworth *et al.*, 1961; Habedank and Thomas, 1970). Cryptorchidism with testicular hypoplasia (Case 5) is a well recognized complication of arhinencephaly with callosal agenesis (the 'olfactogenital dysplasia' of de Morsier, 1954).

Aetiological Considerations

From an aetiological point of view the malformations under consideration fall into three groups: chromosomal abnormalities, genetic disorders, and sporadic cases tentatively ascribed to environmental factors. Only two cases in our material showed clear-cut chromosomal aberrations: Case 1 (trisomy 13) and Case 7 (partial trisomy 7). Case 1 was a fairly typical example of alobar holoprosencephaly as frequently encountered in trisomy 13. While most cases of holoprosencephaly with abnormal karyotype form part of Patau's syndrome, isolated cases have also been reported with deletion of the long arm of chromosome 13, ring chromosome 13, trisomy 18, deletion of the short arm of chromosome 18, ring chromosome 18 and with triploidy (Melnick, 1979; Cohen, 1982; Larroche, 1984). On the other hand, not all cases of trisomy 13 are associated with holoprosencephaly, as this chromosomal disorder covers a wide range of malformations (Colacino and Pettersen, 1978).

Relatively little is known about partial trisomy 7 (7q+). It appears to form a well defined syndrome, consisting of microcephaly, facial dysmorphism and limb abnormalities (Vogel, 1977) and our Case 7 conforms to this pattern. Most cases are associated with severe mental retardation (Vogel, 1977; Kunze, 1980), yet we are not aware of any neurological studies. We do not claim that our findings of micrencephaly, arhinencephaly and dentato-olivary dysplasia constitute a typical pattern of lesions in this syndrome. Probably a wide range of malformations will be discovered as more cases are examined.

There was no example of familial occurrence in our material, yet several familial cases of holoprosencephaly apparently inherited as autosomal recessives have been reported (Dominok and Kirchmair, 1961; DeMyer *et al.*, 1963; Hintz *et al.*, 1968). It is also of interest that malformations of the arhinencephaly-holoprosencephaly-callosal agenesis group have been described in Meckel's syndrome (Paetau *et al.*, 1985). Our Case 5 closely resembles the findings reported by these authors, but in the absence of a family history and of polycystic kidneys the diagnosis of Meckel's syndrome cannot be upheld.

Most of our cases belong to the sporadic group. There is no doubt that environmental factors can produce phenocopies of genetic and cytogenetic disorders. Both holoprosencephaly and agenesis of the corpus callosum have been produced experimentally (Dekaban, 1969). In human material the evidence is anecdotal, and in many cases the maternal histories are too deficient for any valid conclusions. One recurrent theme is that of maternal diabetes (Dekaban and Magee, 1958; Dekaban, 1959, Yakovlev, 1959; Robain and Gorce, 1972; our Case 3), but the evidence is far from conclusive. Several cases have been reported before the identification of the trisomies, and the possibility of chromosomal disorders cannot be excluded, particularly in cases of multisystem anomalies.

Conclusions

Arhinencephaly is neither a morphological nor an aetiological entity, but one aspect of a group of complex malformations, the other elements of which are holoprosencephaly and commissural defects. To these may be added cortical malformations, anomalies of the long tracts, hypoplasias of the optic pathways, cerebellar disorders and dentato-olivary dysplasia. Each of these covers a wide range of deviations from the normal, forming a continuous spectrum from extreme to minimal. The permutations of these components are innumerable and each case appears to display some unique features.

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BOOK REVIEWS

Stroke: Pathophysiology, Diagnosis and Management. Volumes 1 and 2. Edited by H. J. M. Barnett, B. M. Stein, J. P. Mohr and F. Yatsu. 1986. Edinburgh: Churchill Livingstone. Price £135.00.

This work appears in two large volumes, is well produced and illustrated, has no less than 68 contributors and an editorial team of international standing. It sets out to provide an encyclopaedic reference text and will no doubt be a commercial success. Yet it is a strangely unsatisfactory book and, in spite of its size, has many deficiencies and omissions. The book is divided into three main sections: pathophysiology, diagnosis and management. In the first section the development of atheroma and disordered thrombosis receive full attention but there is little on the normal or abnormal physiology of the cerebral circulation. Inevitably with so many authors there is needless repetition particularly on the significance of risk factors and on the role of hypertension.

When dealing with diagnosis and investigation the book is at its best and there are full clinical descriptions of the symptomatology of vascular lesions at various sites suitably illustrated by the latest scanning and angiographic techniques. Mohr's chapters on lacunar infarction and the posterior cerebral artery syndromes are particularly good and contain a well balanced mix of neurological and neuropsychological data. There are also good accounts of lobar haematoma and other haemorrhagic syndromes and of the vertebrobasilar ischaemic syndromes by Caplan and on the cardiac causes of stroke. There is an overview of diagnostic studies again by Mohr and an excellent chapter on CT scanning by Savoiardo.

The major criticism is the narrow view taken on the whole subject of stroke; certainly atherosclerosis is the major underlying arterial disorder but is not the only one. Although there are chapters on cardiac and haematological causes of stroke the treatment of the following topics, all very relevant to cerebral vascular disease, is either inadequate or missing altogether: systemic lupus erythematosus and thrombocytopenic purpura, cerebral complications of Marfan's syndrome, polycythaemia, sickle cell disease, Fabry's disease, herpes zoster, cerebral malaria, homocystinuria, the whole topic of arterial occlusions in pregnancy and in children. Inadequate space is given to the topic of vascular dementia and there are only sketchy descriptions of corticocavernous fistula, fusiform aneurysm of the basilar artery or cavernous aneurysm of the carotid. Although some of these topics are unusual they should certainly be included in a text of this size which will be consulted by general physicians dealing with cerebral vascular disease in its widest aspects.

There is a long chapter on the surgical management of extracranial occlusive disease which is uncritical and didactic and fails to discuss impartially the evidence for and against surgery. In the prevention of stroke by the treatment of risk factors, little evidence is presented to show the effectiveness of therapy other than antihypertensive treatment.

For future editions I would suggest fewer contributors and firmer editing.

R. W. Ross Russell

Surgery of Occlusive Cerebrovascular Disease. By R. S. A. Lord. 1986. Oxford: Blackwell Scientific Publications. Price £72.50.

Surgery for stroke is under increasingly close scrutiny at this time. The ECIC bypass study bravely put a popular surgical treatment to the test of a randomized trial and found that it served patients no

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better than medical management. Crucially, this overall conclusion also applied to those patients whose angiographic lesions and symptoms seemed to reflect a haemodynamic instability that provided the most obvious justification for the procedure. Carotid endarterectomy, the rationale of which is based both on haemodynamic arguments and on ulcerative atheromas as an embolic source, is now also being subjected to prospective trials. That in the UK and Europe has already entered 750 cases, and a similar study is scheduled in the USA.

What can a single surgical monograph do to help those interested in this field, appearing as it does between the ECIC trial and the endarterectomy studies? Dr Lord has written a commendably lucid text which is impressive in its coverage of the scientific background to the subject and in being up to date. For surgeons there is much on the detail of investigation and technique and here the illustrations and diagrams are of excellent quality.

The whole discussion of rationale, of indications for surgery and results is, however, bedevilled by the lack of high quality data pending the new trials. This book, like the two-volume treatise on the same topic by Fein and Flamm, will be valuable to vascular surgeons learning their trade, but general readers may feel the ground is shifting under their feet, and that we should all 'wait and see'.

M. J. G. HARRISON

Motor Control Mechanisms in Health and Disease. Advances in Neurology, Volume 39. Edited by J. E. Desmedt. New York: Raven Press. Price £179.50.

This large and expensive book has 112 contributors and deals with physiological aspects of motor control in man, the chapters being amplified as necessary by the inclusion of data from experimental work in higher animals and primates. The contributors appear to have been given generous allowances of space, and some of them use this to publish or to review quite old data while others present the results of their latest experiments. The reader thus has to be prepared to change gear frequently, but this is a small price to pay for the wide range of experimental techniques and philosophies covered by the book—reflecting, perhaps, that man as an experimental subject can be asked to do very complicated tasks while providing relatively little objective physiological data.

It is remarkable how little of this material is presented to undergraduate or postgraduate students of medicine, but there will now be even less of an excuse for this omission than there was before. Some of the experimental techniques could be used more widely in more straightforward clinical contexts and in the analysis of the process of recovery and rehabilitation from injury to the nervous system. For the present, Bach-y-Rita's chapter gives a tantalizingly brief glimpse of what could follow when this degree of expertise and sophistication is focused on clinical treatment. I know of no other book which can match the range of material presented here and this one is an essential purchase for any neurological or physiological library.

D. L. MCLELLAN

The Frontal Lobes. By Donald T. Stuss and Frank Benson. 1986. Pp. 315. New York: Raven Press. Price $65.50.

The background to this book is provided by the authors' observations on and follow-up of schizophrenics who had undergone prefrontal leucotomy as a treatment for this psychiatric disorder.

The first chapters deal with neuroanatomical considerations, with clinical-neuropathological correlations and with laboratory assessment of frontal lobe disorders. The subsequent 11 chapters deal with different functional categories, and the last 4 chapters with general aspects of frontal lobe function including a final chapter covering the authors' behavioural anatomical theory.

The neuroanatomical considerations provide a short introduction for those readers who are not familiar with the basic neuroanatomy of the frontal lobes. The comparative anatomy of the frontal lobe with particular emphasis on its development in the human is not included. The clinical neuropathological correlations illustrate how different types of pathological processes may affect frontal lobe function, and the chapter on laboratory assessment describes how such processes can be disclosed by the application of various diagnostic techniques.

The 11 chapters on different functional categories cover some of the disorders that are usually attributed to frontal lobe dysfunction such as frontal motor deficits or alterations of attention, awareness, personality, emotion, speech, language and executive systems, but also include sensory perception, visual-spatial functions, cognition and memory—disturbances that are usually seen after lesions of other parts of the brain. The data on the patients with frontal leucotomy are distributed throughout these chapters, and are discussed in the context of other clinical observations, of psychological test procedures or of anatomical and physiological observations on nonhuman primates.

The difficulty with the discussion of the vast literature lies in the immense range of frequently controversial observations. Since anecdotal reports, casual observations and clinical description derived from cases with badly defined lesions are amalgamated with key references it is almost impossible to recognize any consistent pathological features. The authors consequently conclude (p. 138) that 'The concept of a (frontal lobe personality) is woefully inadequate'. In spite of this notion the final chapters represent a synthesis of the present views of frontal lobe function. This part of the book is nicely structured and represents the most interesting part of this treatise on what is possibly the most difficult aspect of brain function.

H.-J. FREUND

Alzheimers Disease and Related Dementias. By M. Roth and L. L. Iversen. 1986. Pp. 116. Edinburgh: Churchill Livingstone, for the British Council. *British Medical Bulletin*, January 1986. Price £16.00.

I have spent several enjoyable hours reading this number of the *British Medical Bulletin* and I am certain it will remain for me a very useful source of information for a long time to come. Important changes in our understanding of Alzheimer's disease have occurred in the last ten years and many of those who made the most outstanding contributions have been brought together in this volume to give us a critical appraisal of the advances that have taken place in their fields. The book contains papers on clinical aspects, epidemiology, genetics, electrophysiology, neuropathology, biochemistry, neurotransmitters and aspects of management. There is much which is excellent in this slim volume and to single out one contribution seems unfair to the rest. Thus I felt equally interested when reading about epidemiology or the assessment of patients, topics which often receive an unimaginative treatment, than when reading about the recently described neurotransmitter or neuropathological abnormalities. I found the review of pharmacological treatments useful and the hypothesis put forwards to relate Alzheimer's and Parkinson's diseases intriguing. The editors should be congratulated for assembling this excellent volume which will be of great interest to the many professionals engaged in research or in the management of the disease.

MARIA A. RON

Optic Neuritis. Edited by R. F. Hess and G. T. Plant. 1986. Pp. 310. Cambridge University Press. Price £35.00.

The editors, in their preface to this book, suggest that it 'represents the first step of the scientific and clinical assessment of optic neuritis originally described in detail by Nettleship'. The first claim, perhaps, carries some substance, the latter is manifestly absurd. Indeed there is a strong sense, having read the book, that the clinical data have been introduced almost as an afterthought in an attempt to produce a more comprehensive text. The biophysical aspects of normal and disordered vision are part of a rapidly expanding, and increasingly technical, area of knowledge and it is clearly in this area that the editors are more at ease. The clinical chapter comprise some 35 pages in a text reaching to nearly 300. A brief chapter on optic neuritis in childhood, obviously intended to reappear as a paper, is more a summary of the authors' study of the subject than an attempt at a comprehensive appraisal of the literature. The whole of the clinical spectrum of optic neuritis is reduced to a single chapter. The reduction is such that the editors decision to include, as an appendix, extensive quotations from Nettleship's 1884 paper on retro-ocular neuritis provides more clinical data than is available in the rest of the text.

The clinical chapter is not without error. In particular, it is suggested that 'in acute isolated optic neuritis examination of the cerebrospinal fluid (CSF) rarely shows a cellular response or raised total protein'. The statement is contradicted elsewhere in the text. In fact in four papers recording the CSF findings in isolated optic neuritis a raised protein concentration was found in between 24 and 49%, and an abnormal cell count in between 33 and 51% of cases.

The larger part of the book, devoted to research aspects of the subject and its electrophysiological evaluation, is uneven. Two chapters, describing an animal model of virus-induced demyelination, represent an exhaustive account of personal work rather than a survey of the literature. Similarly, in the chapter on visual evoked potentials in acute optic neuritis, emphasis is placed on a report of personal work concerning changes in the evoked potentials during the clinical course of optic neuritis in 22 patients. Editorial inconsistency is evident here, since the authors' statement that 'due to the frequent absence of observable acute signs, diagnosis of optic neuritis always presents severe difficulties' (which, of course, is quite untrue) is contradicted by the editors elsewhere. The weight of the book is concentrated in chapters on the immunological aspects of optic neuritis and contributions on the psychophysical loss in optic neuritis and its electrophysiological assessment. Whilst the language in the immunological chapter is lucid, that in the others is at times depressingly obscurantist. Examples such as 'its role (psychophysics) is to translate the dysfunction which characterizes the condition into a neurophysiologically meaningful code' are not unique. Such infelicities simply further restrict rather than enhance understanding of the subject.

The book, therefore, fails in its stated aims. Its appraisal of the clinical aspects of the subject is inadequate and perfunctory. The chapters devoted to research aspects of optic neuritis vary widely in quality and the value of the more substantial chapters is often diminished by the limitations imposed by their language.

There is a final point. The editors, on page 304, ask for any information on the test of Ole Bull, quoted by Nettleship. Further details of this test of colour vision are given in Nettleship's *The Student's Guide To Disease Of The Eye*, Fourth edition (1887), London: Churchill, pp. 431–432.

G. D. Perkin

Paediatric Neurology. Second edition. By Ingrid Gamstorp. 1985. Pp. 411. London: Butterworths. Price £35.00.

Textbook of Child Neurology. Third edition. By John H. Menkes. 1985. Pp. 827. Philadelphia: Lea and Febinger. Price $64.25.

These two well-known books on paediatric neurology have appeared in new editions. Each reflects the special experience of its author. Gamstorp's is alive with pictures of children; and advice on management distilled from an obviously rich clinical experience of everyday problems in paediatric neurology is easy to find—how to help the parents of a malformed or stillborn baby, the practicalities of choosing a treatment for periodic paralysis and the management of cerebral palsy or muscular dystrophy are far more real to the reader here than in Menkes' book. But the text is brief, clinical descriptions are lively rather than detailed and the coverage of the treatment of the epilepsies, for example, is almost threadbare in comparison with that in Menkes.

Menkes' text is nearly three times as long. It is extensively referenced in the text; while Gamstorp gives only a selected bibliography after each chapter Menkes lists 789 references on metabolic diseases, 280 on heredodegenerative ones, 475 on malformations, 711 on infections, and so on. It is very difficult to write with wisdom and style while quoting and referencing on this scale but Menkes manages pretty well. His new edition maintains the high reputation gained by the previous ones (1974, 583 pages; 1980, 695 pages) and as a handy encyclopaedia it is probably the best available of the half dozen books in the field. A new chapter has been added on the neurological manifestations of systemic disease (including particularly useful sections on metabolic, cardiac and neoplastic disorders) and the whole book has been brought up to date with new material on ultrasound MRI and PET imaging and on the use of recombinant DNA techniques, and in many other ways. Finding areas to criticize is not difficult, as in any text written almost entirely by one author. For example, muscle disorders are clearly not Menkes' special area of interest, but these are more than compensated for by the high overall standard and the unrivalled expertise he has (as an author of a textbook) in the field of neurometabolic disease.

Gamstorp's book is far more digestible and would be a good choice as a book to read through for an overview of the most important and frequent clinical problems in child neurology. It can be recommended for a ward text or for a students' library while Menkes' book is definitely a postgraduate text for the more experienced paediatrician and the reference library.

D. GARDNER-MEDWIN

Clinical Neurosurgery, Volume 32. Proceedings of the Congress of Neurological Surgeons, New York, 1984, 1985. Pp. 680. Baltimore: Williams and Wilkins. No price stated.

A multiauthor book on a neurosurgical topic is almost always a disappointment and seldom seems worth the considerable purchase price paid. The series 'Clinical Neurosurgery', based on the proceedings of the annual congress of neurological surgery is a splendid exception to this depressing general rule. Volume 32 of the series based on the 1984 Congress in New York is outstanding even by the standards set by its predecessors.

The 32 chapters are arranged in 7 sections. The first two chapters consist of reminiscence of the posthumous honoured guest of the Congress, Walter Dandy by his living cohonoured guest Dr Hugo Rizzoli. The succeeding sections cover a variety of topics—Cerebrovascular Surgery, Tumours of the Cerebellopontine Angle and their Management, Trigeminal Neuralgia, Pineal Tumours, Orbital Tumours, and Hydrocephalus.

Virtually every chapter can be read both for pleasure and instruction. The texts are in general well edited and clear, the type is easy on the eye, the illustrations first class and the binding strong enough to withstand the rereadings which much of this volume deserves. It is a pleasure for a reviewer to be able to recommend a neurosurgical book without reservations. If a neurosurgeon has to choose one book a year to buy he should without doubt buy *Clinical Neurosurgery*. By itself the annual volume of *Clinical Neurosurgery* should be sufficient to keep him in touch with the main stream of developments in his speciality.

R. S. MAURICE-WILLIAMS

FORTHCOMING EVENTS

Thirteenth International Symposium of the Fulton Society

This Symposium, which will be on 'Memory' will be held in association with the Annual Meeting of the American Neurological Association to be held in San Francisco on October 18–21, 1987. Further information may be obtained from Dr Victor Soriano, Calle Buenos Aires 363, Montevideo, Uruguay.

Joint Meeting of the Brain Research Society and the Alzheimer's Disease Society on Alzheimer's Disease

A meeting on the pathology, neurochemistry, and molecular biology of Alzheimer's disease will be held in Southampton on July 22–24, 1987. Further information may be obtained from John Hardy, Department of Biochemistry, St Mary's Hospital Medical School, London W2 1PG, or Peter Roberts, Department of Pharmacology, University of Southampton, Southampton SO9 3TU.

Sandoz Foundation for Gerontological Research

This Foundation has been established by Sandoz Ltd., Basel, Switzerland, to mark its centenary year and the strong commitment that Sandoz has to gerontology. The aim of the Foundation is to encourage new and innovative research concerned with problems of ageing and the ageing individual. Financial assistance will be offered towards the support of particular projects. For further information, contact Dr Leo Abisch, Secretary, Sandoz Foundation for Gerontological Research, Sandoz Ltd., Region III, CH-4002 Basel, Switzerland.

Fyssen Foundation 1987–1988 Fellowships

The general aim of the Fyssen Foundation is to encourage all forms of scientific enquiry into cognitive mechanisms, including thought and reasoning, underlying animal and human behaviour, into their biological and cultural bases and into their phylogenetic and ontogenetic development. For this purpose, the Foundation will award a certain number of fellowships for the training and support of research scientists working in disciplines relevant to the aims of the Foundation such as ethology, palaeontology, archaeology, anthropology, psychology, epistemology, logic and the neurosciences.

The fellowships will be granted to French scientists wishing to work abroad and to foreign scientists wishing to work in French laboratories. Study grants will normally be given for one year but may be extended up to three years. Applications should be made on a form obtainable from the Foundation and should include a curriculum vitae, a list of the applicant's publications, the names of two senior scientists whom the applicant has asked to send testimonials to the Secretariat of the Foundation, and a letter of acceptance from the inviting laboratory.

Completed applications (15 copies) should be sent to the Secretariat of the Foundation, 194 rue de Rivoli, 75001 Paris. Applications must be received by April 1, 1987.

First Northern Lights Neuroscience Symposium

This symposium, organized by the Scandinavian Society of Neuropathology, will be held at the University of Bergen, Bergen, Norway, on May 20–23, 1987. It will focus on myelin and demyelination. Review lectures will be delivered by internationally recognized experts and communications or poster presentations on the biology and pathology of myelin will be welcomed. The closing date for submission of abstracts is February 20, 1987. Further information may be obtained from the NLNS Secretariat, PB 113, N-5014 Bergen, Norway.

Gordon Holmes Lecture

The third Gordon Holmes Lecture, endowed by the Guarantors of *Brain*, will be delivered on June 3, 1987 at 5 p.m. in the Kennedy Lecture Theatre, Institute of Child Health, London, by Dr L. P. Rowland of the New York Neurological Institute. It will be entitled 'The Impact of Molecular Genetics on Clinical Neurology'. Admission is free, without ticket.

The Fourth Annual Morris Bender Memorial Lecture

This will be delivered by Dr D. Carleton Gajdusek, Nobel Laureate and Chief, Central Nervous System Studies Laboratory, National Institutes of Health, on April 6, 1987 at 4 p.m. in the Stern Auditorium, Annenberg Building, The Mount Sinai School of Medicine. The subject will be 'Transmissible and nontransmissible dementias in amyloidosis of the brain'.

CORRECTION

R. Kaji *et al.*: Origin of short latency somatosensory evoked potentials to median nerve stimulation in the cat: comparison of the recording montages and effect of laminectomy. *Brain*, **109**, 443–468.

The authors of this paper wish to correct an error in fig. 1. In the scalp-NC recording for the cat, the right-hand wave of the two labelled 'p13a' should have read 'p13b'.

Travel Grants
For Young Neuroscientists

The Guarantors of *Brain* are prepared to consider applications for contributions towards travel costs from neuroscientists under the age of 40 working in the United Kingdom.

1. The primary purpose of such grants is to facilitate short visits to laboratories or departments of particular relevance to the applicant's research. Applications cannot be entertained without the following documents:
   - (a) an abbreviated curriculum vitae and a list of any relevant publications;
   - (b) statement of age and post currently held;
   - (c) a concise account of the purpose of the proposed visit;
   - (d) a recommendation from the head of department (where appropriate);
   - (e) a letter of acceptance from the department to be visited;
   - (f) a statement of costs likely to be incurred, and of other applications for funds that have been made. Advantage should always to taken of reduced air fares when available.
2. Applications will also be considered for contributions to the cost of attending specialized symposia of particular importance to the applicant's research. Documents as in (a), (b), (c), (d) and (f) above should be submitted at least three months before the date of the meeting, accompanied by a statement of what other applications for financial aid have been made and of any contributions by the symposium organization.
3. Only exceptionally will applications for assistance to attend larger international congresses be entertained.

Successful applicants will be expected to submit a brief report on the conclusion of their visit.

Four copies of all documents should be submitted to

Dr. M. J. G. Harrison
Reta Lila Weston Institute of
Neurological Studies,
Middlesex Hospital Medical School,
London W1N 8AA

Reduced Subscription Rates

A reduced subscription rate (£20.00 per annum) is available to young subscribers under the age of 40 years, who are in a training post in clinical neurology or in the neurosciences in the UK. Applications for this special rate should be made to Dr. M. J. G. Harrison, The Middlesex Hospital, Mortimer Street, London, W1N 8AA with a letter from the head of department confirming the applicant's eligibility.

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Brain

A JOURNAL OF NEUROLOGY

VOLUME 110 · PART II · APRIL 1987

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Hereditary generalized amyloidosis with polyneuropathy: clinicopathological study of 65 Japanese patients. Shu-ichi Ikeda, Norinao Hanyu, Minoru Hongo, Jiro Yoshioka, Hisao Oguchi, Nobuo Yanagisawa, Takayoshi Kobayashi, Hiroshi Tsukagoshi, Nobuo Ito and Tadaaki Yokota 315

Gustatory hallucinations in epileptic seizures: electrophysiological, clinical and anatomical correlates. C. Hausser-Hauw and J. Bancaud 339

Disturbance of sequential movements in patients with Parkinson's disease. R. Benecke, J. C. Rothwell, J. P. R. Dick, B. L. Day and C. D. Marsden 361

Pure word deafness following bilateral lesions: a psychophysical analysis. Yasufumi Tanaka, Atsushi Yamadori and Etsuro Mori 381

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Orientation-selective visual loss in patients with Parkinson's disease. D. Regan and C. Maxner 415

Stretch and vibration reflexes of wrist flexor muscles in spasticity. F. W. J. Cody, Helen C. Richardson, N. MacDermott and I. T. Ferguson 433

Localization, timing and specificity of gating of somatosensory evoked potentials during active movement in man. Leonardo G. Cohen and Arnold Starr 451

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Regional threshold contrast sensitivity within the central visual field in optic neuritis. Gordon T. Plant and Robert F. Hess 489

Physiological and behavioural consequences of seizures induced in the rat by intrahippocampal tetanus toxin. John G. R. Jefferys and Sarah F. Williams 517

Peripheral sensorimotor and autonomic neuropathy associated with systemic lupus erythematosus. P. A. McCombe, J. G. McLeod, J. D. Pollard, Y.-P. Guo and T. J. Ingall 533

Book reviews 551

Announcements 561

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Book reviews 551

Announcements 561

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Volume 49 (5) Extrapyramidal Disorders

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CONTENTS: Foreword. 1. Anatomy of the basal ganglia *(M. B. Carpenter, Bethesda, MD)*. 2. The relationship of the basal ganglia to the limbic system *(H. J. W. Nauta, Baltimore, MD)*. 3. Chemistry of the basal ganglia *(D. B. Calne and W. R. W. Martin, Vancouver, Canada)*. 4. Clinical neuropharmacology of the basal ganglia *(A. R. Cools, Nijmegen, The Netherlands)*. 5. Clinical pathophysiology of basal ganglia disease *(I. Kanazawa, Ibaraki-ken, Japan)*. 6. Parkinson's disease: clinical features and etiopathology *(A. Barbeau, Montreal, Canada)*. 7. Juvenile parkinsonism *(H. Narabayashi, M. Yokochi, R. Iizuka, Tokyo, Japan, and T. Nagatsu, Nagoya, Japan)*. 8. Parkinsonism-dementia *(K.-M. Chen, Tamuning, Guam, and Th. N. Chase, Bethesda, MD)*. 9. Drug-induced movement disorders (tardive dyskinesia and dopa-induced dyskinesia) *(C. M. Tanner, Chicago, IL)*. 10. Striatonigral degeneration *(R. D. Adams and M. Salam-Adams, Boston MA)*. 11. Acquired hepatocerebral syndromes *(M. Salam-Adams and R. D. Adams, Boston MA)*. 12. Wilson's disease *(J. M. Walshe, Cambridge, UK)*. 13. Progressive supranuclear palsy *(A. N. Barr, Chicago, IL)*. 14. Huntington's chorea: etiology and pathogenesis *(E. D. Bird, Belmont, MA)*. 15. Huntington's chorea *(G. W. Bruyn and L. N. Went, Leiden, The Netherlands)*. 16. Neuropathology of Huntington's chorea *(R. A. C. Roos, Leiden, The Netherlands)*. 17. Chorea-acanthocytosis *(G. W. Bruyn, Leiden, The Netherlands)*. 18. Chronic juvenile hereditary chorea (benign hereditary chorea of early onset) *(G. W. Bruyn, Leiden, The Netherlands, and N. C. Myrianthopoulos, Bethesda, MD)*. 19. Paroxysmal choreoathetosis *(O. J. S. Buruma and R. A. C. Roos, Leiden, The Netherlands)*. 20. Sydenham's chorea, chorea gravidarum and contraceptive induced chorea *(P. A. Nausieda, Milwaukee, WI)*. 21. Ballism *(O. J. S. Buruma, Leiden, The Netherlands, and J. P. W. F. Lakke, Groningen, The Netherlands)*. 22. Athetotic syndromes *(M. Salam-Adams and R. D. Adams, Boston, MA)*. 23. Neuroaxonal dystrophy: its relation to aging and neurological diseases *(F. Seitelberger, Vienna, Austria)*. 24. Striopallidodentate calcifications *(A. Lowenthal, Wilrijk, Belgium)*. 25. Dentato-rubro-pallido-luysian atrophy *(R. Iizuka, Tokyo, Japan, and K. Hirayama, Chiba, Japan)*. 26. Pallidal, pallidonigral and pallidoluysionigral degenerations including association with thalamic and dentate degenerations *(K. Jellinger, Vienna, Austria)*. 27. Exogenous lesions of the pallidum *(K. Jellinger, Vienna, Austria)*. 28. Hereditary putaminal necrosis (Paterson) *(K.-F. Druschky, Erlangen, FRG)*. 29. (Exogenous) striatal necrosis *(K. Jellinger, Vienna, Austria)*. 30. Dystonia musculorum deformans *(G. W. Bruyn and R. A. C. Roos, Leiden, The Netherlands)*. 31. Diurnally fluctuating hereditary progressive dystonia *(M. Segawa, Y. Nomura, and M. Kase, Tokyo, Japan)*. 32. Symptomatic dystonias *(R. A. C. Roos and G. W. Bruyn, Leiden, The Netherlands)*. 33. Chorea: differential diagnosis *(G. Padberg and G. W. Bruyn, Leiden, The Netherlands)*. 34. Essential - familial tremor *(R. R. Young, Boston, MA)*. 35. Differential diagnosis of tremor *(M. Hallett, Bethesda, MD)*. 36. Tremor: its generating mechanism and treatment *(H. Narabayashi, Tokyo, Japan)*. 37. Myoclonus *(M. Hallett, Bethesda, MD, C. D. Marsden, London, UK, and S. Fahn, New York, NY)*. 38. Tics: Gilles de la Tourette syndrome *(Ch. G. Goetz, Chicago, IL)*.

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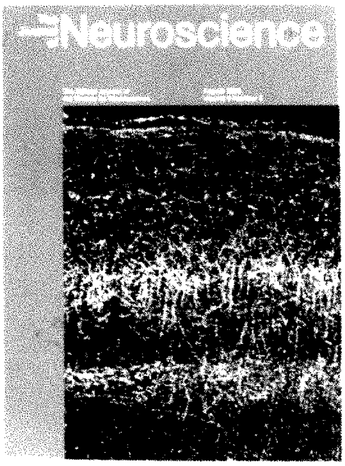

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THE MUTANT *mdx*: INHERITED MYOPATHY IN THE MOUSE

MORPHOLOGICAL STUDIES OF NERVES, MUSCLES AND END-PLATES

by L. F. B. TORRES *and* L. W. DUCHEN

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SUMMARY

The *mdx* mutant mouse was first observed during a survey of genetic variations of pyruvate kinase in the mouse. Affected mice have high serum levels of this enzyme and although showing little disability they have widespread and severe muscle disease. Light and electron microscopy, muscle enzyme histochemistry and combined cholinesterase-silver impregnations were used for the study of affected and control animals aged 1 day to 1 year. An early ultrastructural abnormality present already at 1 day was scattered focal streaming of Z-lines. Later there was also segmental muscle fibre necrosis and regeneration. The proportion of muscle fibres showing either necrosis, regeneration or internal nuclei was assessed in several muscles, at ages ranging from 10 days to 1 year. Acute segmental necrosis and regeneration were most marked at 1 to 2 months, although they were present at all ages. The number of fibres with internal nuclei increased progressively until 3 months when 70–80% showed this abnormality. Nerve terminals were unaffected but there was a reduction in the number and depth of post-synaptic folds at motor end-plates in adult animals, confirmed by morphometric analysis. Quantitative study of L4 motor root and tibial nerve showed that fibre numbers, axonal calibres and myelin sheath thickness were normal at all ages. No qualitative abnormalities were found in the CNS or other organs. The findings strongly suggest that the *mdx* mutant has a primary muscle disease and that the nervous system is normal.

INTRODUCTION

Inherited disorders in laboratory animals constitute a valuable source of scientific information. Careful clinical, genetic and pathological studies are necessary in the investigation of a new mutant since if features are discovered which are similar to those expressed in human disease, the mutant might become a useful model for experimental investigations which are not possible in man (Grüneberg, 1956). Animals with inherited neuromuscular disease (the 'neurological mutants') were described by Grüneberg (1956), Sidman *et al.* (1965), Green (1966) and Harris (1979). A recent listing (*Mouse News Letter*, 1986) catalogued about 100 mouse

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mutants in which the behavioural signs and the investigations indicated a neurological disorder amongst over a thousand genetically determined diseases. In most neurological mutants in the mouse, however, the peripheral nervous system as well as skeletal muscle have shown abnormalities. Since in the human muscular dystrophies, such as the Duchenne type, there is no definitely known involvement of the nervous system (Dubowitz and Crome, 1969; Tomlinson *et al.*, 1974), the availability of a purely myopathic disease (i.e., one affecting only skeletal muscle) in a small laboratory animal would be of particular interest. Bulfield *et al.* (1984) reported a new mutant mouse (*mdx*) with an X-linked inherited muscle disease and very high levels of serum pyruvate kinase. Since the few published morphological studies were restricted only to muscle pathology (Bulfield *et al.*, 1984; Dangain and Vrbova, 1984; Tanabe *et al.*, 1986; Karpati *et al.*, 1986) it seemed important to study this mutant more extensively. This paper describes qualitative and quantitative observations on the *mdx* mouse in which a special study has been made of the evolution of the disease and the question of involvement of the nervous system.

MATERIAL AND METHODS

Animals

Several *mdx* breeding pairs were sent by Dr G. Bulfield from the Poultry Research Centre, Midlothian, Scotland. Since this is an X-linked disease, and affected animals remain fertile, all females received were homozygous for the *mdx* gene and males (normally carriers of a single X chromosome) were also affected. A special breeding diet (CRM diet, Labsure Ltd) and tap water were supplied ad libitum. Young mice were weighed weekly and were fed an expanded diet softened by reconstituted milk powder.

All animals were examined daily. Neurological and muscular abnormalities were assessed by observing spontaneous activity, ability to walk and hold on to a wire grid, the grid-bars being about 1–2 cm apart.

Litter number and mortality. Thirty litters (169 mice) from homozygous *mdx* pairs were followed. The number of pups at birth and after 4 weeks was recorded. The results were compared with data obtained from 13 litters (135 mice) of control animals.

Weight. Twelve litters from *mdx* pairs (45 mice) were studied. All animals were identified by an ear mark and weighed weekly for four weeks. The results were compared with data from 5 litters of controls (a total of 30 mice).

A total of 71 *mdx* aged 1 day to 18 months and 40 C57BL/10 controls matched for age and sex were studied by histological, histochemical and electron microscopic techniques.

Morphological Methods

Under anaesthesia mice were perfused through the left ventricle with fixative.

Paraffin histology. The fixative used was formol-calcium (10% formalin in 1% calcium acetate) followed by FAM (formaldehyde—1 part; glacial acetic acid—1 part; methanol—8 parts). After fixation the mice were decalcified in formic-citrate and cut into transverse 3–5 mm slices at standard anatomical levels so that many areas of head, trunk and limbs could be examined (Beesley and Daniel, 1956). Sections were stained with haematoxylin-eosin, haematoxylin-van Gieson, silver impregnation for axons (Marsland *et al.*, 1954) and luxol fast blue for myelin combined with cresyl violet for nerve cells (Klüver and Barrera, 1953).

Cholinesterase activity and axons. These were demonstrated by the methods of Namba *et al.* (1967) and Pestronk and Drachman (1978). Mice were perfused with cold (4° C) formol-calcium. Longitudinal cryostat sections of the calf muscles (gastrocnemius, plantaris and soleus) and anterior muscles of the leg (tibialis anterior and extensor digitorum longus, EDL) were cut at 20 and 30 μm and respectively stained by the acetyl-thiocholine iodide and bromoindoxyl acetate methods to demonstrate cholinesterase, followed by silver impregnation of axons.

Muscle histochemistry. Transverse cryostat sections of fresh unfixed muscles of the leg were stained by Gomori's trichome method and Sudan black, for acid phosphatase and myosin ATPase activity, and for mitochondrial oxidative enzymes (Pearse, 1985).

Electron microscopy. The fixative used was a cold (4° C) freshly prepared modified Karnovsky's (1965) fluid. Blocks were taken from many regions including spinal cord, sensory ganglia, sensory and motor spinal roots, several different muscles, heart, kidneys and, from some animals, all extraocular muscles after their identification. The blocks were then left overnight in fresh fixative, postfixed in 1% osmium tetroxide, dehydrated in ethanol and embedded in araldite. Longitudinal and transverse 1 μm sections were stained with toluidine blue. Ultrathin sections were stained with uranyl acetate and lead citrate.

Teased fibre preparations. Single nerve fibres were isolated for the measurement of internodal length. Tibial nerves were processed as for electron microscopy but left in unpolymerized araldite omitting the accelerator. Under a dissecting microscope the nerve fibres were teased apart on a glass slide with fine dissecting needles. The preparations were made permanent by heating them overnight at 60° C.

Analysis of Muscle Pathology

Distribution of lesions. Twelve individual muscles were selected for special study. These were tibialis anterior, extensor digitorum longus, soleus, lateral and medial heads of gastrocnemius, rectus femoris, biceps and triceps brachii, parascapular, lumbar paravertebral, digastricus, and masseter. The muscles were analysed in 2 *mdx* mice at each of 6 different ages, 1.5, 3, 5 and 7 weeks, 3 months and 1 year. The number of necrotic fibres, regenerating fibres and fibres with internal nuclei were counted and at least 600–700 fibres analysed in each muscle. A random square sampling technique (Mayhew and Sharma, 1984*a*, *b*) was used.

Muscle fibre diameter. The diameter of muscle fibres was measured in transverse frozen sections of unfixed tissue stained with haematoxylin and eosin, the trichrome method, and to demonstrate ATPase activity and oxidative enzymes. Five hindlimb muscles from 1 *mdx* mouse and 1 control at each of 5 different ages (1.5, 3, 4 and 5 weeks and 9 months) were analysed. Under light microscopy, using a drawing tube which projected over the bit-pad of a Kontron MOP image analyser, a cursor with a light-emitting diode was used to trace the outline of at least 70–100 fibres per muscle. The MOP was linked to an RML 380Z computer programed to calculate fibre diameter assuming circularity. Results were displayed in histogram form to show size frequency distribution of all fibres as well as of fibre types 1 and 2.

Peripheral Nerves

Total numbers of nerve fibres. Fibres were counted in L4 motor root and tibial nerve in 1 *mdx* mouse and 1 control at each of 5 ages (14, 25, 46, 75 and 180 days). The root was identified by following the sciatic nerve up to the spinal cord, the thickest contributing root being labelled as L4. The root and nerve blocks were embedded in araldite and 1 μm transverse sections stained with toluidine blue. The total cross-sectional area of the root or nerve was measured by use of the projection tube, bit-pad and cursor (as described under muscle fibre diameter). Ultrathin sections were examined in the electron microscope and photographed at a magnification of 5000 (calibrated by means of a grating replica, 2160 lines/mm). All areas of these nerves which were not obscured by grid bars were photographed. Myelinated and unmyelinated fibres in the prints (enlarged × 3) were counted and the total area photographed was calculated (usually only about 15–20% of the nerve). The total number of fibres in the nerve was then calculated from the cross-sectional area.

Fibre diameter. Total fibre diameter (axon+myelin sheath) and myelin sheath thickness were measured on enlargements (final magnification 2880) of photographs of the toluidine blue-stained sections taken under ×40 oil immersion. At least 400 fibres were measured in each nerve using the cursor, bit-pad and computer as described above, assuming axonal circularity.

Internodal length. This was measured in teased single fibres of tibial nerve from 1 *mdx* and 1 control aged 75 days; 3–8 sequential internodes on at least 50 fibres from each nerve were measured and correlated with fibre diameter following the method of Fullerton *et al.* (1965).

Motor End-plates

Morphometric analysis of a number of parameters (Table 1) defined by Engel and Santa (1971) and Santa and Engel (1973), was made of neuromuscular junctions observed in transverse ultrathin sections of soleus. The grids were adjusted in the electron microscope specimen chamber to a standardized height and the magnification calibrated with a grating replica. Every end-plate region observed in step-sections at 100 μm intervals over approximately 1 mm was photographed and prints enlarged to a final magnification of 20000. Each profile of an axonal terminal, considered as an individual end-plate, and the related postsynaptic membrane were analysed with the help of an image analyser linked to a RML 380Z computer as previously described.

RESULTS

Clinical Observations

The *mdx* mice were carefully observed over long periods of time. Some were examined daily from soon after birth until 1 year of age. The affected mice, even the homozygous females, showed surprisingly little obvious disability. Some showed a mild degree of muscle weakness as demonstrated by their not clinging as strongly to the bars of a wire grid as did the normals. Affected animals, both male and female, were fertile and able to breed but there seemed to be more litters lost among the *mdx* compared with controls. The numbers in each litter and the mortality amongst the young mice were noted. The *mdx* litters had a significantly smaller number of pups (average 5.6 in 30 litters) than controls (average 10.4 in 13 litters) and there was a higher mortality rate (average 3.4 per litter) than normal (average 1 per litter) during the first four weeks.

The body weights of *mdx* mice and controls during the first four weeks were obtained by weekly weighing of about 45 *mdx* and 30 control mice. No significant differences were found.

Morphological Observations

Extensive histological examination was made of *mdx* mice from 1 day of age, to many months, and of age-matched controls. The use of the serial-block technique for embedding tissues in paraffin wax facilitated the study of all viscera and many levels of the CNS, and in no instance was any abnormality in organs (including the heart) observed. Furthermore, myelination in brain and spinal cord was normal in extent and sensory ganglion cells also appeared normal (though they were not counted). The skeletal muscles were affected by the most striking pathological changes, and the analysis of these changes, and of the innervation of muscle, forms the major part of this report.

Skeletal Muscle

In the *normal mouse* the morphology of skeletal muscle, as examined with both light and electron microscopy, follows that of other mammalian species very closely. Enzyme histochemical preparations demonstrate the same types of fibre classified according to their reactivity as types 1 and 2 as in other mammalian muscle fibres (Brooke and Kaiser, 1970; Dubowitz and Brooke, 1973). In the mouse the muscle fibres are already well advanced in maturity by the time of birth and fibre types are fully expressed within 10–14 days of age (Dubowitz, 1968; Platzer, 1978; Wirtz *et al.*, 1983).

Light microscopy. Light microscopy of the *mdx* muscles showed some differences from normal even at day 1 after birth. Scattered occasional fibres were rather large, rounded, eosinophilic and also had a glassy homogeneous appearance. These fibres seemed to be fewer in the limb muscles than in the cranial and axial musculature. By 5 days there was necrosis of muscle fibres and invasion by phagocytes especially in muscles of the head and shoulder girdle (fig. 1). The pathological changes increased in extent and severity and by 10 days clusters of necrotic fibres, many invaded by macrophages, and small regenerating fibres with basophilic cytoplasm and vesicular

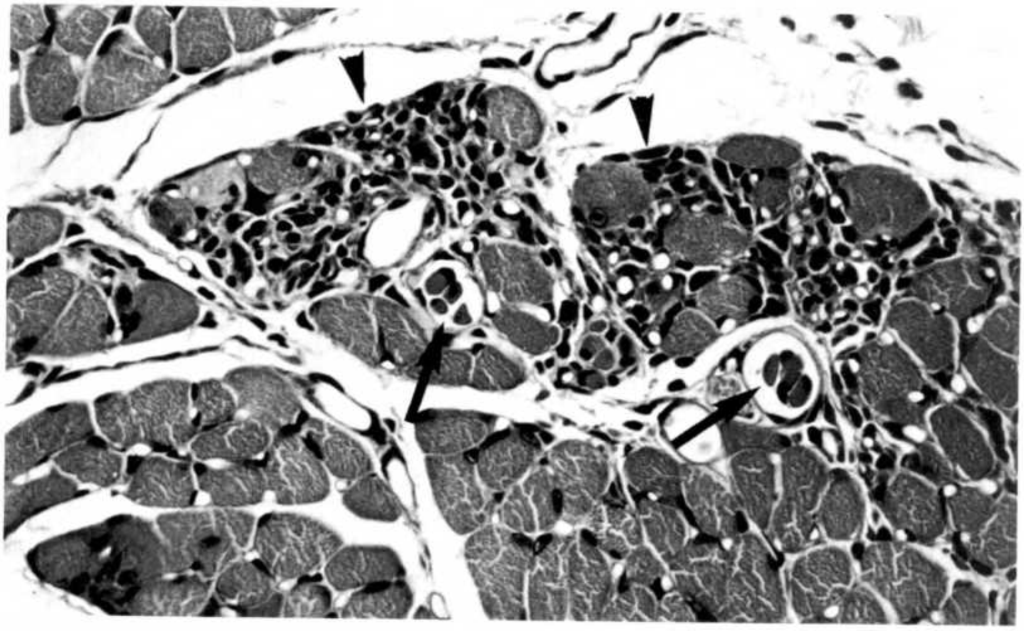


FIG. 1. Section of parascapular muscle of 5-day-old *mdx* mouse. Muscle fibres undergoing degeneration and phagocytosis are shown (arrowhead). Muscle spindles (arrows) appear normal. The remaining muscle fibres are normal in appearance and do not have central nuclei. Haematoxylin-eosin, × 400.

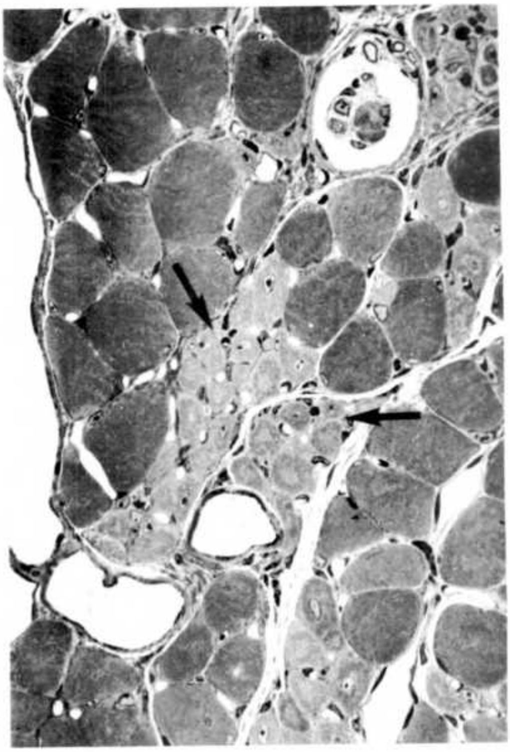
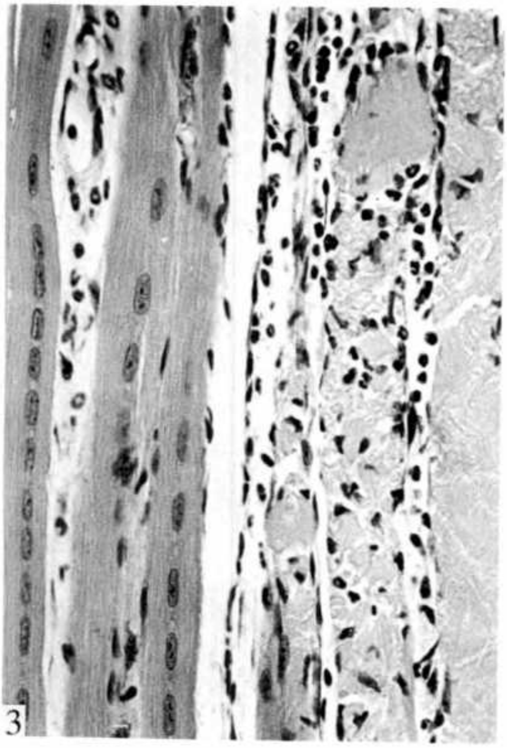


FIG. 2. Soleus muscle of a 5-week-old *mdx*. Small, round regenerating fibres (arrows) containing vesicular central nuclei with prominent nucleoli occupy a large proportion of some fascicles. Most other muscle fibres and a spindle are unaffected. Toluidine blue, × 400.

nuclei containing prominent nucleoli, were present. From then on the degenerative process was progressively more severe, necrosis reaching a peak at 5–6 weeks of age, characteristically affecting clusters of fibres or even whole fascicles. There was little or no increase in endomysial connective tissue or replacement of muscle tissue by fat in the *mdx* in contrast to Duchenne muscular dystrophy in man, in which these changes become marked during the progression of the disease. Examples of the various pathological appearances of muscles are shown in figs 2–5. In some preparations it seemed that the lesions affected the two sides of the body symmetrically. There were occasional foci of calcification in the pathological muscles. The muscles of the head, trunk and limb girdles were more severely affected in the early stages than limb musculature but with increasing age, virtually all muscles became affected more or less to the same degree.

Electron microscopy. A very extensive study of the *mdx* muscles by electron microscopy did not reveal any single specific pathology which could help to elucidate the underlying disease mechanisms. Many different muscles were sampled at ages ranging from 1 day to 1 year and included those innervated by cranial nerves (e.g., tongue, masseter, extraocular muscles), axial muscles (intercostal, diaphragm, paravertebral) and forelimb and hindlimb muscles (biceps and triceps brachii, soleus, extensor digitorum longus, tibialis anterior, gastrocnemius). No specific inclusions such as nemaline rod bodies or tubular aggregates and no mitochondrial



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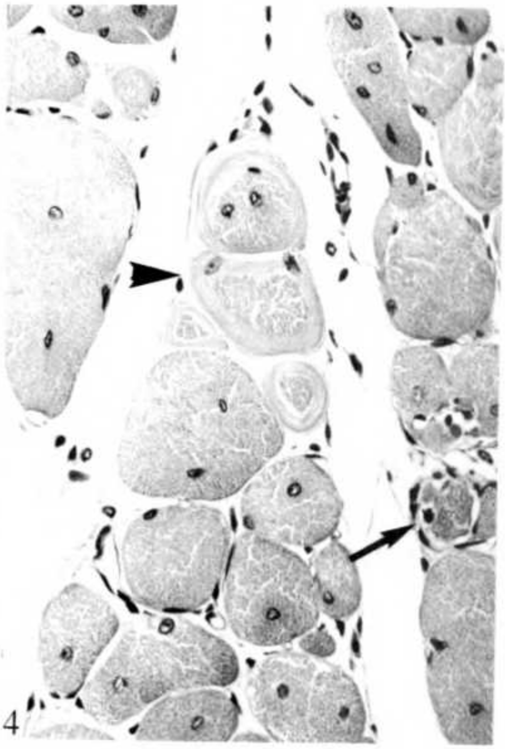

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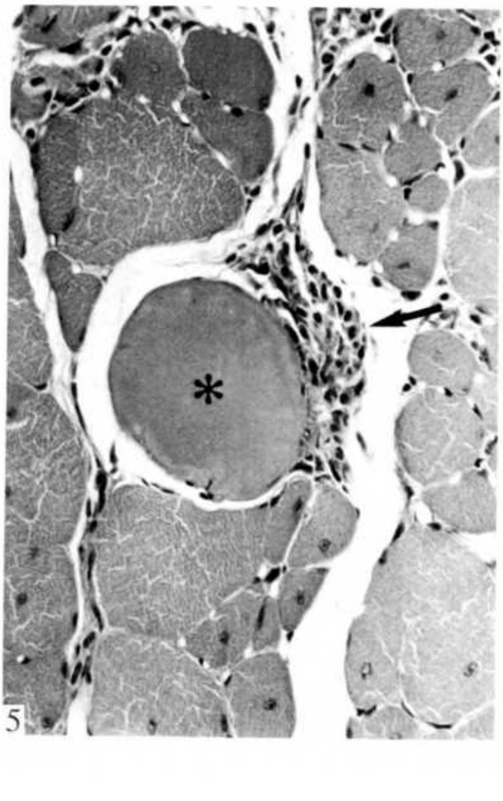

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FIGS 3–5. Sections of hindlimb muscles of adult *mdx* mice. The longitudinal section (fig. 3) shows acute necrosis, macrophage invasion, regeneration and rows of internal nuclei. The transverse sections (figs 4, 5) show marked variation of fibre diameter, internal nuclei in most fibres, ring-forms (arrowhead) and various degrees of acute degeneration represented by hyaline fibres (*) and necrotic fibres (arrow). Haematoxylin-van Gieson, × 400.

pathology such as paracrystalline inclusions were found. The characteristics of fibre necrosis and regeneration were very much as described in other conditions as reviewed by Cullen and Mastaglia (1982). No 'delta' lesions, of the kind described by Mokri and Engel (1975), were observed. In all instances where severe muscle fibre disorganization had occurred the basal lamina always remained intact.

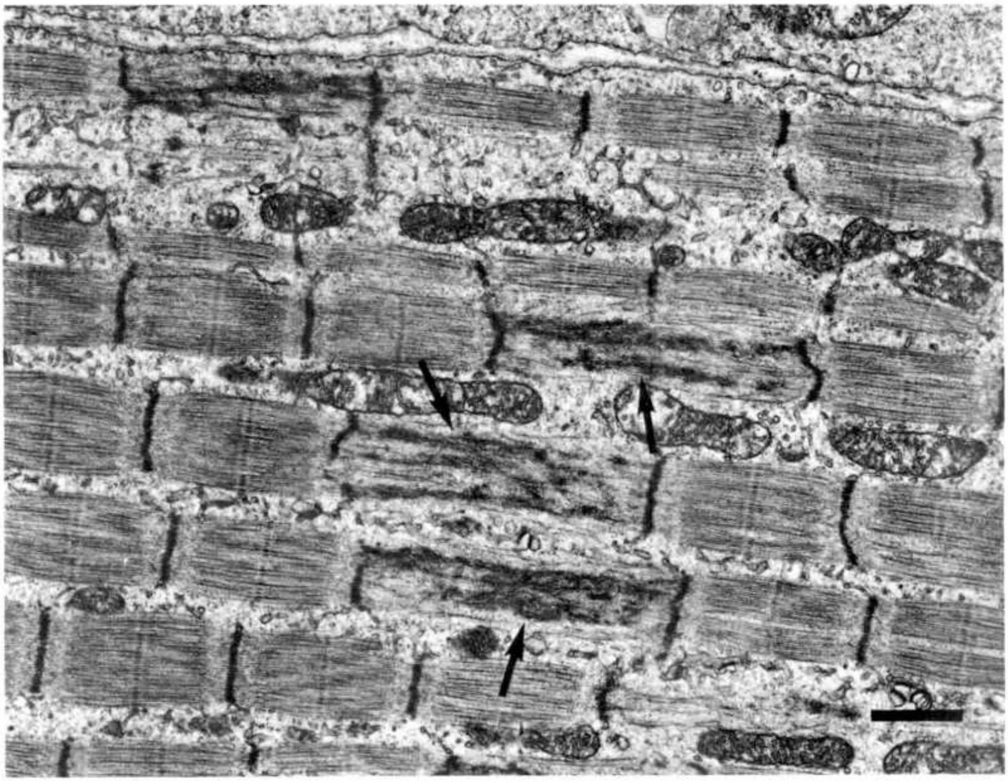


FIG. 6. Electron micrograph of soleus of *mdx* 1 day after birth. Occasional Z-lines of individual myofibrils are disrupted and two adjoining sarcomeres disorganized (arrows). Bar = 1 μm.

What the electron microscopy did reveal was the constant presence in many muscles, even at 1 day postnatally, of an early disorganization of Z-lines (fig. 6). This was the earliest pathological change that has thus far been identified. The disorganization took the form of a spreading out ('streaming') of Z-line material from a single Z-line over two adjacent sarcomeres in one, or several, myofibrils. The process seems to spread progressively to affect more sarcomeres and more myofibrils until much of the contractile apparatus of the muscle fibre becomes disorganized. The degeneration affects only a segment of the fibre longitudinally but the whole width of the fibre in the transverse plane. A later stage is the formation of an amorphous 'retraction clot' (fig. 7) among which there may be visible degenerating mitochondria and remnants of dilated sarcoplasmic reticulum. In some fibres dilated cisternae were present and probably occur in the early stages of degeneration. The plasmalemma was seen to be intact even when there was severe internal disorganization but it eventually became disrupted in a discontinuous fashion (also shown in fig. 7), leaving the basal lamina intact.

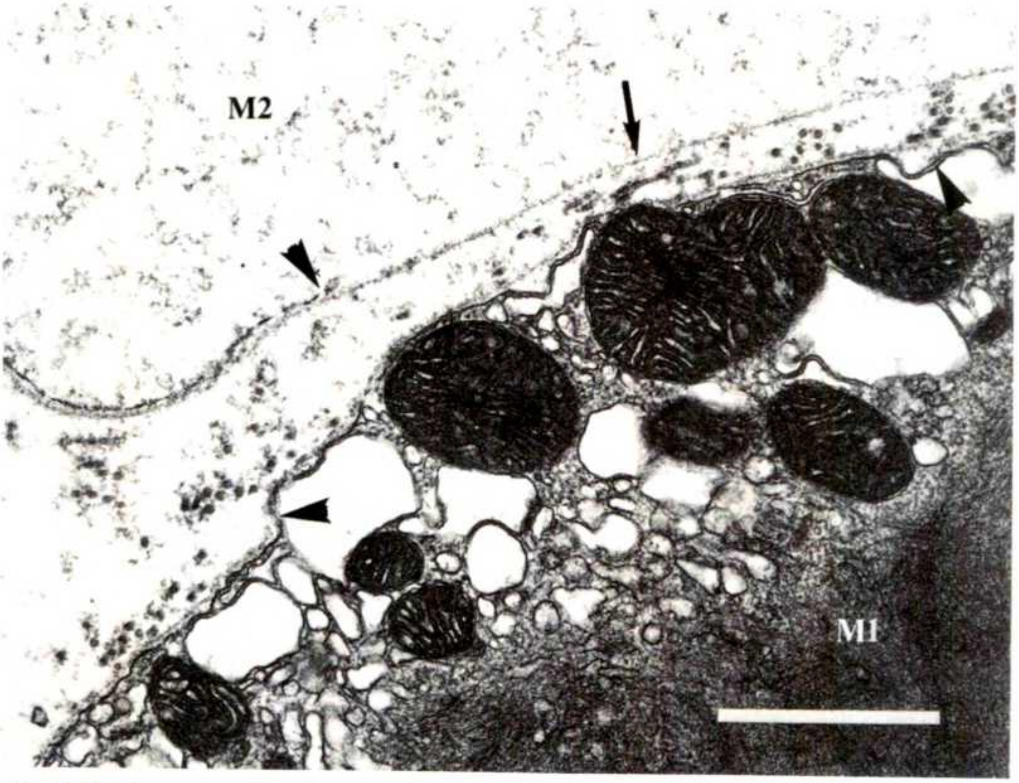


FIG. 7. Tibialis anterior of 5 weeks *mdx*. The plasmalemma of a necrotic fibre (M1) is still intact (arrowheads) whereas in an adjacent fibre (M2), also showing severe internal disruption, the plasmalemma is discontinuous (arrowhead) but the basal lamina (arrow) remains intact. Bar = 1 μm.

The reaction and invasion by macrophages and the other characteristics of regeneration, namely proliferation of satellite cells with the formation of myoblasts, myotubes and eventually new muscle fibres, has been well reviewed by Mauro *et al.* (1970) and Carlson (1973), and in the *mdx* the appearances were very much like those previously described.

Muscle fibres with central (internal) nuclei as well as peripheral subsarcolemmal nuclei became more numerous with age. It is likely that these fibres had previously been necrotic and had regenerated. In a number of instances in adult animals, streaming of the Z-lines, indicative of early degeneration, was taking place in muscle fibres which already contained central nuclei (fig. 8). This implies that the degeneration may occur at different times, even repeatedly, in the same muscle fibre. The central nuclei, although they occurred in rows, were separated from each other by sarcoplasm or a varying number of sarcomeres. This separation would help to explain why, in transverse paraffin sections, there was usually about 20% of fibres in which the section did not pass through internal nuclei. A common finding in muscles of adult animals was the presence of very tiny muscle fibres adjacent to abnormally large fibres.

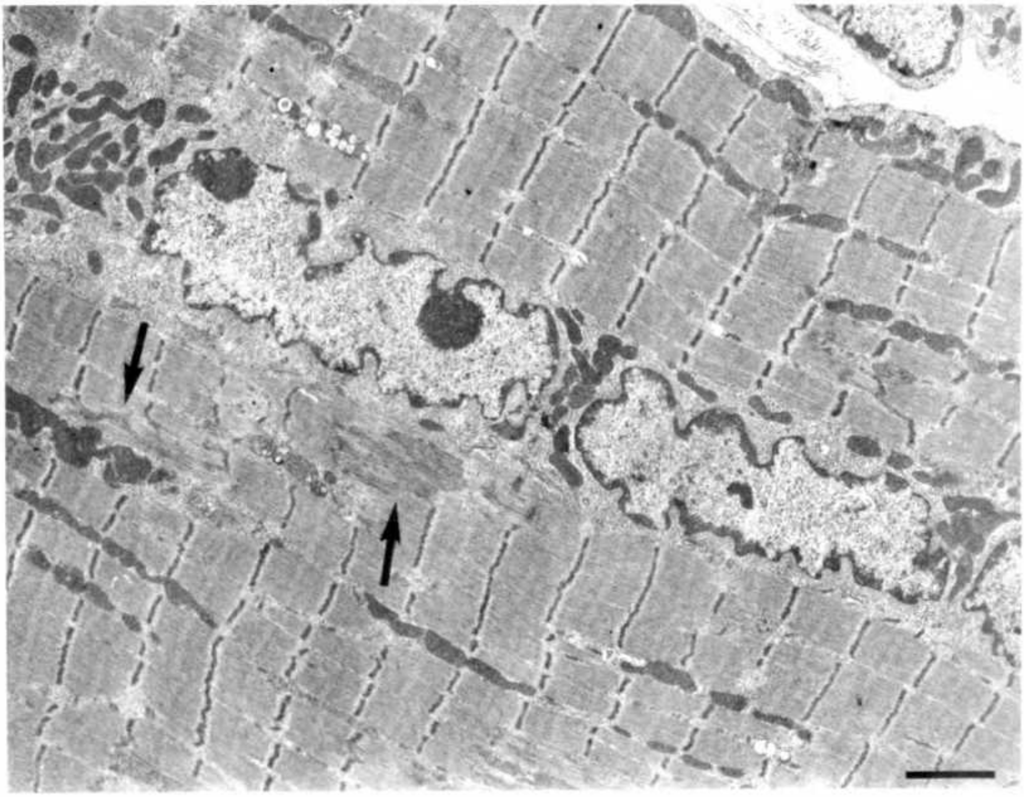


FIG. 8. Electron micrograph of hindlimb muscle of 7-week-old *mdx*. A row of internal nuclei and Z-line streaming (arrows) are present in the same muscle fibre. This appearance suggests that a fibre which has already been necrotic and regenerated may become necrotic again. Bar = 2 μm.

In view of the observations by Karpati *et al.* (1982, 1986) that necrosis did not occur in denervated and atrophied fibres in the dystrophic hamster and in *mdx* mouse, an attempt was made to see whether necrosis was less common in small as compared with large diameter fibres. This was found to be a very difficult problem since it was not possible to assess the original diameter of a fibre which was clearly necrotic. Furthermore, the identification of early Z-line abnormalities is best seen in longitudinal sections studied by electron microscopy, a plane which precludes the accurate evaluation of muscle fibre diameter.

Heart muscle, extraocular muscles and muscle spindles. These were examined in many *mdx* animals at different ages. In none of these has any pathological change been identified.

Evolution of pathological change. In order to compare the evolution of the pathology in various muscles, the abnormal muscle fibres were divided into three classes—necrotic, regenerating and those with internal nuclei (implying previous necrosis and regeneration). The results of this analysis are shown in fig. 9 in which the increasing proportion of abnormal fibres is apparent in every muscle examined. It seems, however, that some muscles, particularly the parascapular, and to a lesser extent, paravertebral and tibialis anterior, contained a higher proportion of abnormal fibres by 3 weeks of age, the parascapular reaching 65% of fibres which are abnormal. In the fully developed *mdx* 70–80% of fibres contained internal nuclei. Necrosis and regeneration, varying somewhat from muscle to muscle, were present throughout the life-span of the animals.

Muscle fibre diameter. Measurements of muscle fibre diameters showed a markedly excessive variation which ranged from the very small (less than 10 μm) to much larger than normal (up to 140 μm) compared with a range of 20–70 μm in the normal. An example illustrating the evolution of the variation in fibre diameter is shown in fig. 10, which shows the fibre size distribution in tibialis anterior at 3 weeks, 5 weeks and 9 months.

Histochemistry. Histochemical staining of enzyme activity was undertaken to determine if one type of muscle fibre was selectively affected by the disease. Muscle fibres were classified according to Brooke and Kaiser (1970) and Dubowitz and Brooke (1973). Type 1 fibres showed strong oxidative enzyme reactivity and were also strongly stained by the myosin ATPase reaction at pH 4.6 and 4.3. The fibres which react strongly for myosin ATPase at pH 9.5 were classified as type 2, being further subdivided into type 2A (negative ATPase at pH 4.6 and moderate oxidative enzyme activity) and 2B which were weakly positive for ATPase at pH 4.6. The histochemical preparations of *mdx* muscle showed that both the very small fibres and the large were of all types and many contained internal nuclei (fig. 11). The results of the measurements of fibre diameter are shown in fig. 12 in which size-distribution histograms of fibre types 1 and 2 are plotted in tibialis anterior of *mdx* and controls. It can be seen that a greatly increased spectrum of fibre diameter in *mdx* affected both types of muscle fibre. A similar result was obtained in soleus. It seems clear that the disease process in *mdx* does not selectively affect one or other type of muscle fibre.

Motor Innervation of Muscle

Innervation pattern. The pattern of innervation of skeletal muscle in the mouse closely follows that of other mammalian muscle (Bowden and Duchen, 1976). Mixed

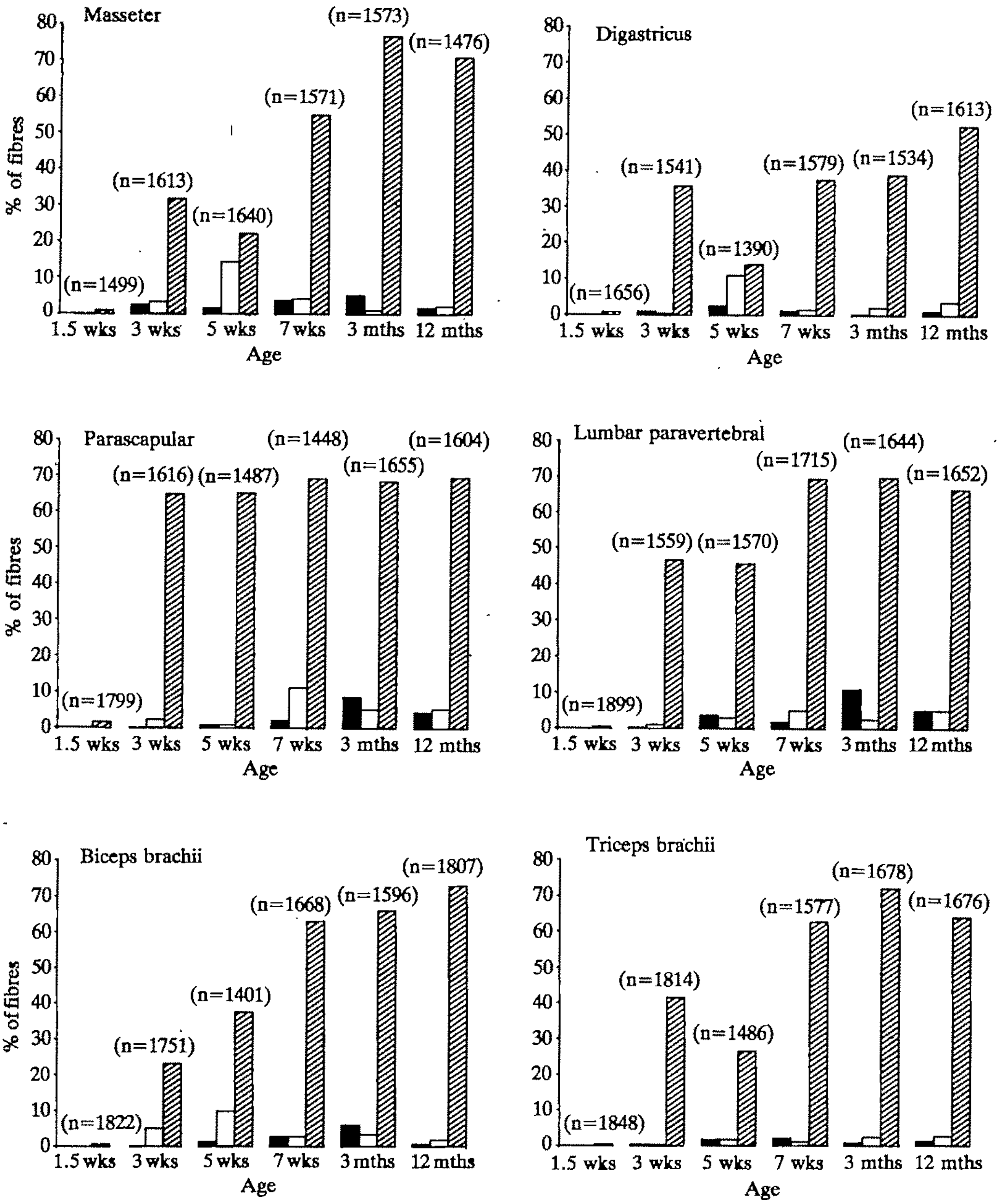
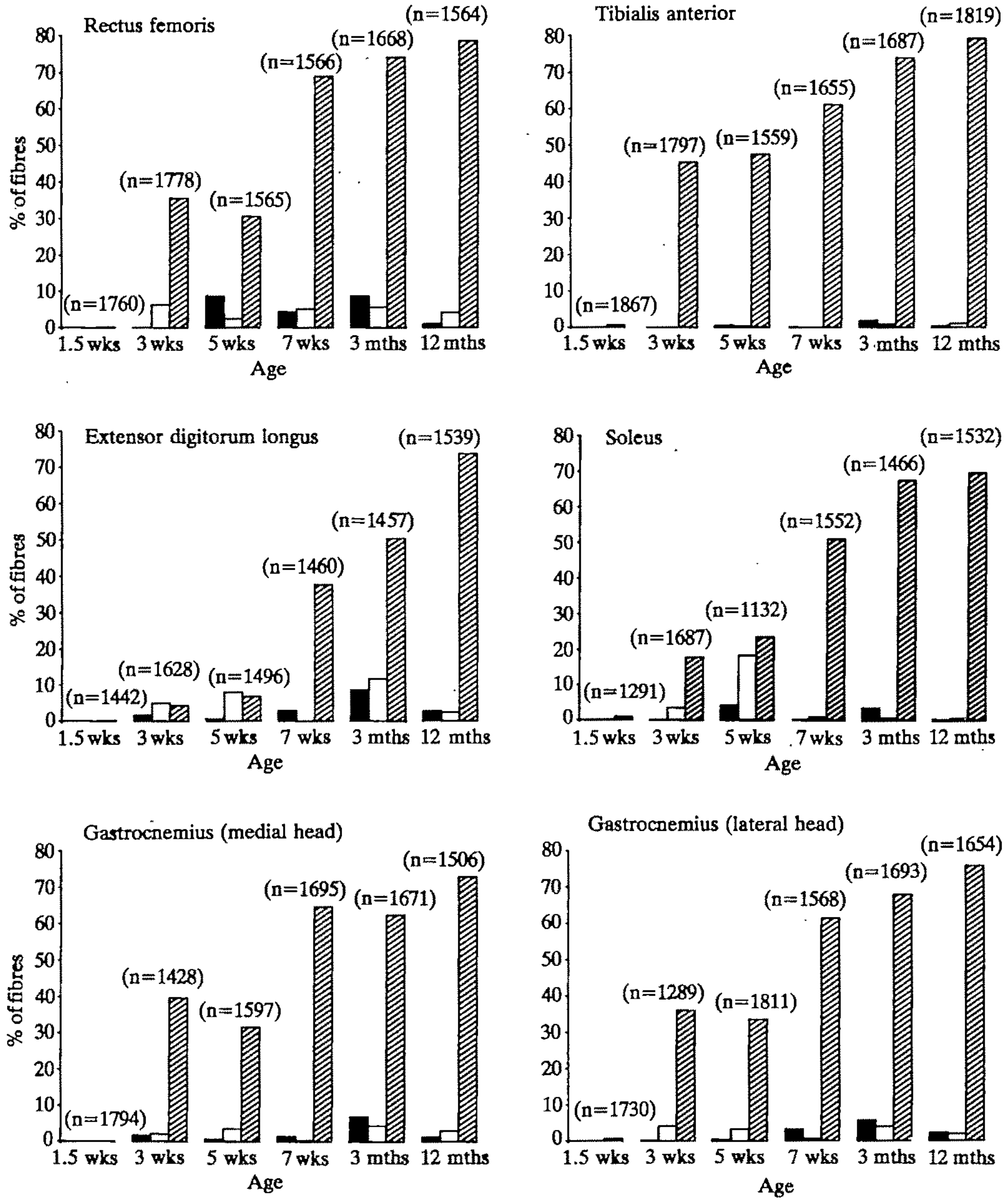


FIG. 9. (*Continued on following page.*) Histograms showing frequency distribution of necrotic fibres (solid bars), regenerating fibres (open bars) and fibres with internal nuclei (hatched bars) in 12 different muscles of *mdx* mice. Each muscle was studied in transverse paraffin sections in 2 animals at each of the 6 different ages shown. The total number of muscle fibres counted at each age is shown in brackets.



motor and sensory nerves penetrate the muscle at the neurovascular hilum and after branching repeatedly reach the middle of the muscle. At this point the nerve bundles break up into a spray of single myelinated preterminal axons, each innervating a single muscle fibre at a single end-plate. The preterminal axon loses its myelin sheath shortly before entering the end-plate where it forms a delicate terminal arborization.

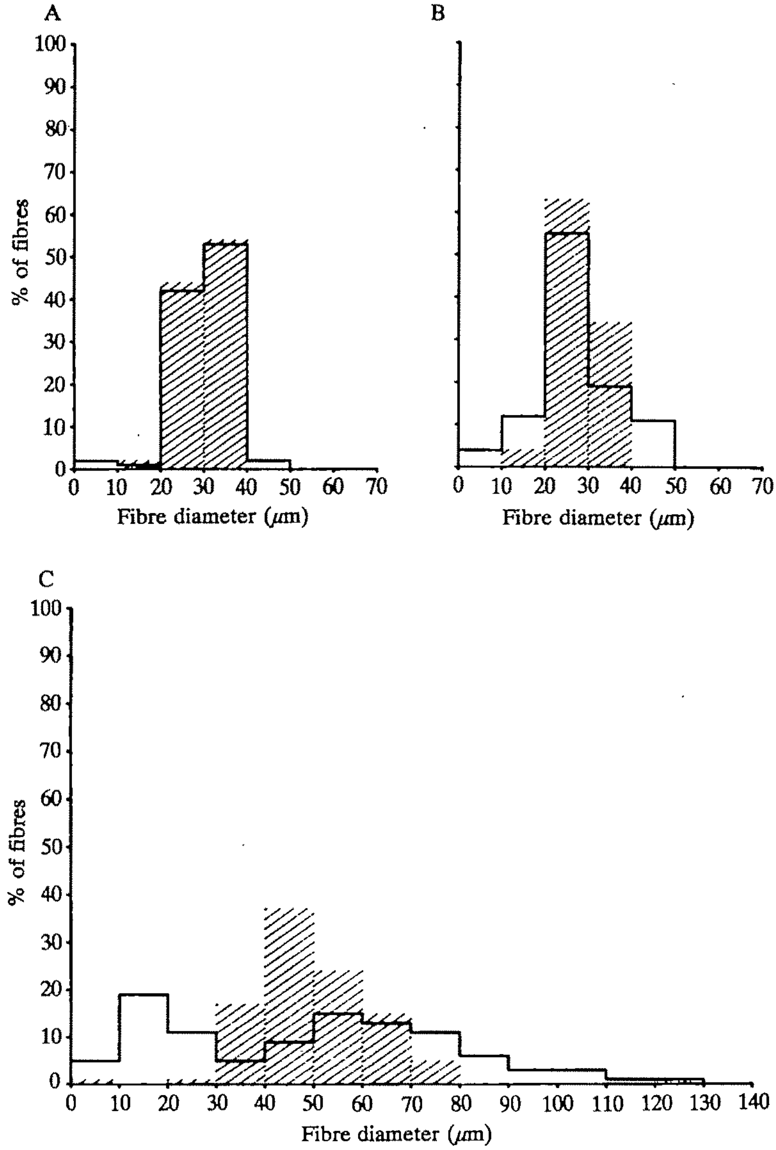


FIG. 10. Fibre size distribution in tibialis anterior of *mdx* (open bars) and control (hatched bars) at 3 weeks (A), 5 weeks (B) and 9 months (C) of age. At least 100 fibres were measured on frozen sections of each muscle. By 5 weeks of age some increase in variation of muscle fibres is already present. In adult diseased animals the variation in size becomes marked with diameters ranging from less than 10 μm to 130 μm.

Cholinesterase activity is concentrated in the gutters of the end-plate formed by indentation of the postsynaptic membrane. Electron microscopy of the normal neuromuscular junction has been extensively reviewed by Padykula and Gauthier (1970), Engel and Santa (1973), Bowden and Duchen (1976) and others. The axonal

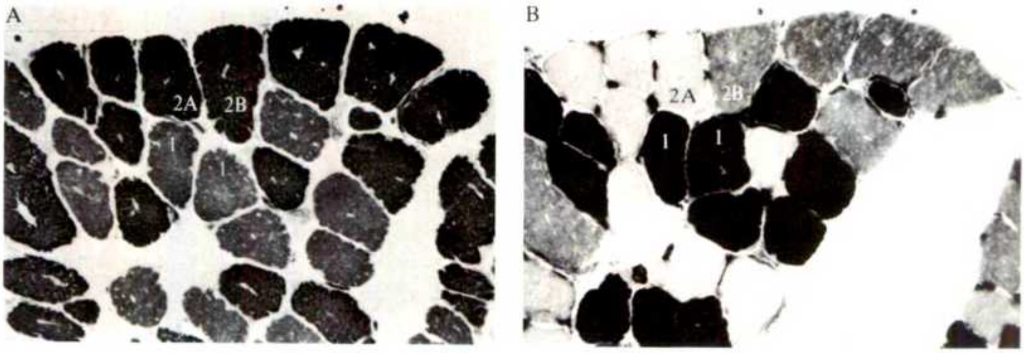


FIG. 11. Serial frozen sections of soleus muscle of an adult *mdx* stained to demonstrate myosin ATPase at pH 9.5 (A) and pH 4.6 (B). Persistent internal nuclei are present in all types of fibre. Examples of type 1, 2A and 2B fibres are indicated. × 400.

terminal (containing synaptic vesicles and mitochondria) lies in a depression of the sarcolemma which is markedly infolded. The external surface of the axonal terminal is covered by Schwann cell cytoplasm and basal lamina fills the gap between axon and muscle and extends into the postsynaptic folds. There is usually a collection of large 'sole-plate' nuclei, with prominent nucleoli, beneath the end-plate and this area of sarcoplasm is rich in organelles and usually devoid of fibrils.

The innervation of muscle in *mdx* was studied in frozen sections of leg muscles at various ages ranging from 4 weeks to 1 year. At no stage was there a disturbance of the pattern of innervation, the nerve bundles breaking up into the expected spray of

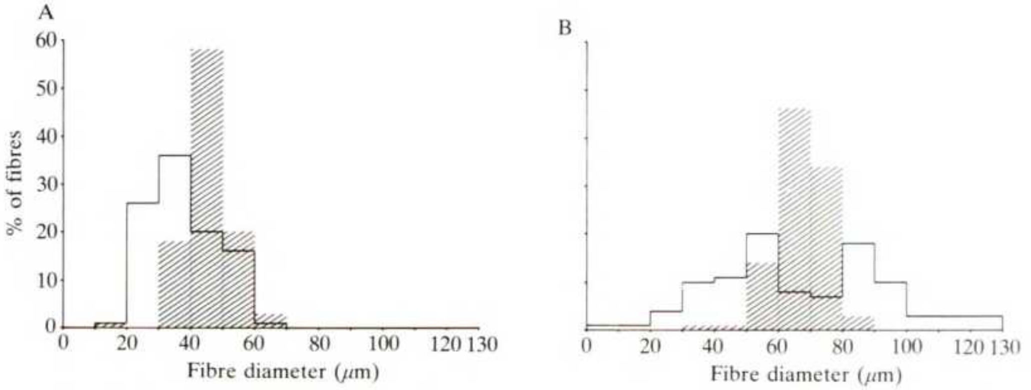


FIG. 12. Histograms showing variation of muscle fibre diameter related to fibre types in tibialis anterior of *mdx* (open bars) and control (hatched bars) at 9 months of age. A, type I fibres; B, type II fibres. Measurements were made in transverse frozen sections stained to demonstrate myosin ATPase pH 9.5. In *mdx* very small fibres (< 10 μm) are of both type 1 and 2. Very large fibres are usually type 2.

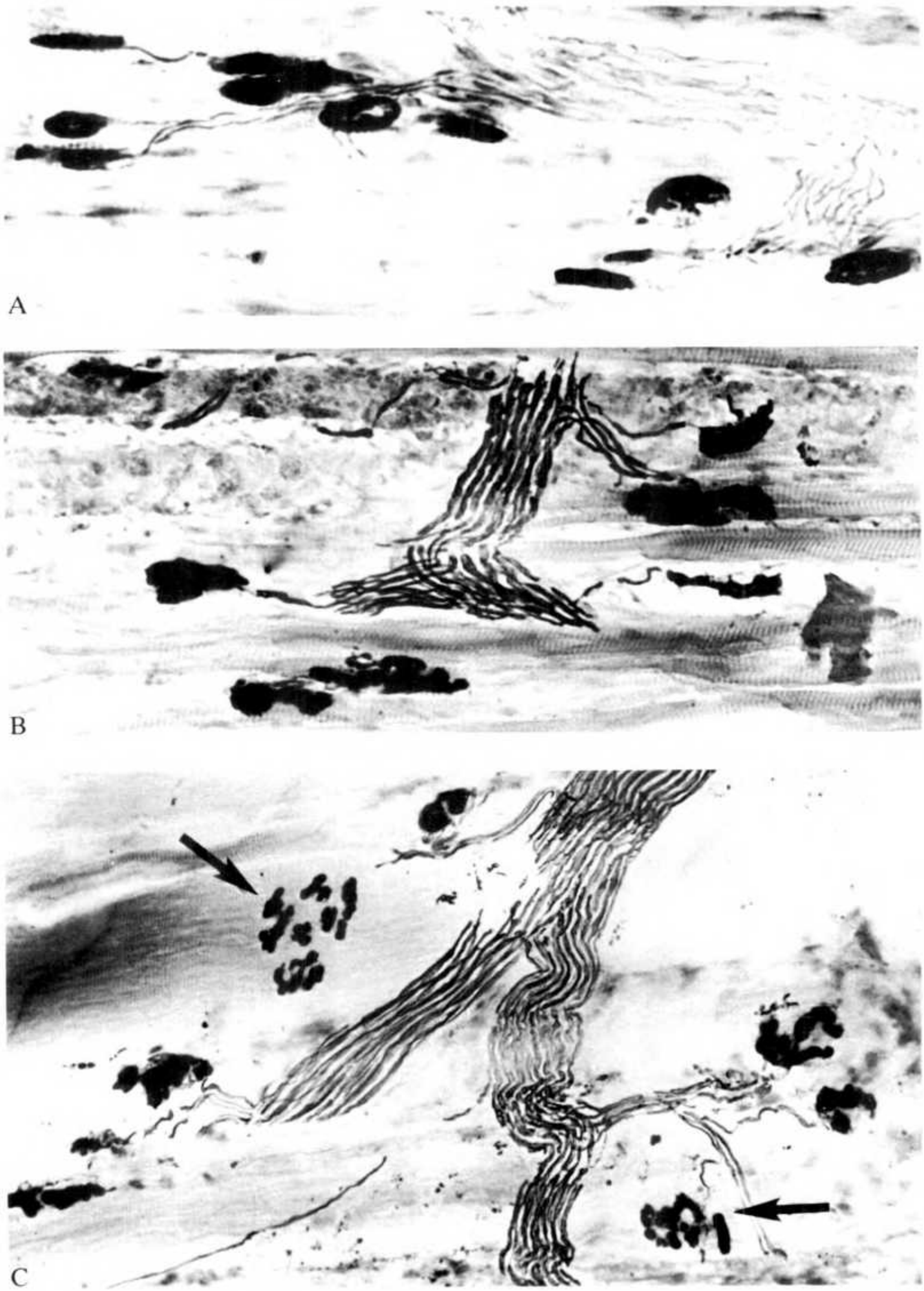


FIG. 13. Frozen sections of soleus of *mdx* mice aged 4 weeks (A), 7 weeks (B) and 4 months (C). The nerve bundle and pattern of distribution of preterminal axons is normal. Cholinesterase activity is localized as in the normal in young animals (A). With increasing age the end-plates become progressively more broken up into small subunits (arrows in C). Cholinesterase-silver method of Namba *et al.* (1967). A, ×400; B, ×350; C, ×280.

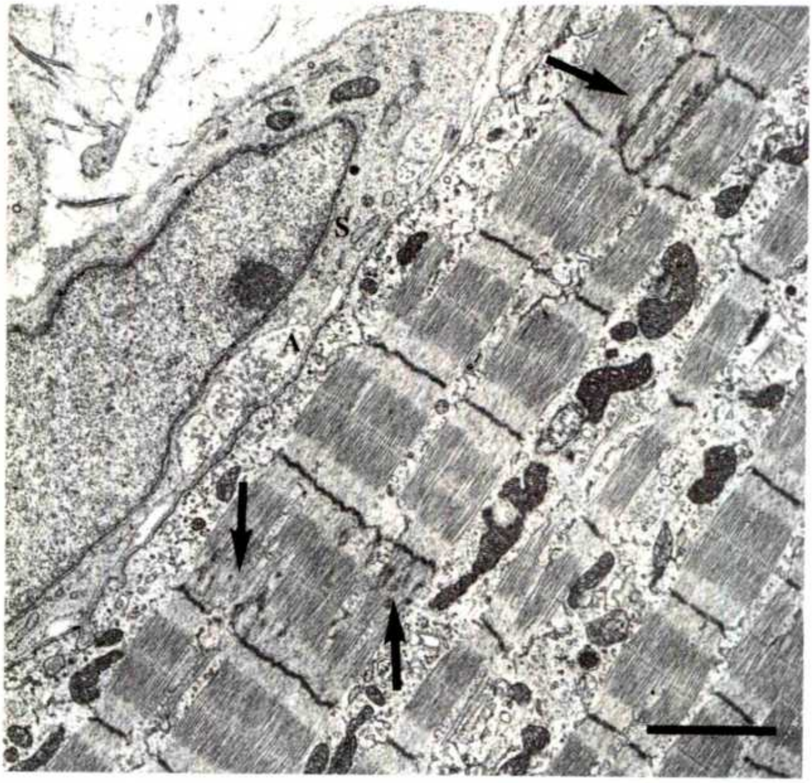


FIG. 14. Electron micrograph of soleus of 1-day-old *mdx*. Small axonal terminals (A) lie in shallow depressions of the sarcolemmal membrane with postsynaptic folding yet to develop. The myofibrils, however, already show evidence of Z-line disorganization (arrows). S = Schwann cell. Bar = 2 μm.

preterminal myelinated axons, each innervating a single end-plate on a single muscle fibre (fig. 13). In the very young animals the cholinesterase activity was well-localized to end-plate gutters which formed continuous lines or rings (fig. 13A) as in the normal. The morphology of individual end-plates, however, became abnormal with increasing survival time. In older *mdx* mice the end-plates, as shown by cholinesterase localization, were broken up into groups of small spots or cups (fig. 13C) where enzyme activity was concentrated, even though each group of these small subunits was innervated by a single preterminal axon. No axonal sprouting, either collateral or ultraterminal, was noted at any stage.

Electron microscopy of neuromuscular junctions. A very extensive study in *mdx* muscles was also undertaken, the animals studied ranging in age from the first post-natal day to 1 year old. The early development and maturation of end-plates in *mdx* was comparable to that in the normal controls. The axonal terminals, small at first, lay in shallow grooves and postsynaptic infolding of sarcolemma was poorly developed (fig. 14). The primary synaptic cleft increased in depth steadily, axonal terminals increased in size and postsynaptic folds became more numerous and deeper over the next few weeks. At 3–4 weeks the adult pattern of end-plate morphology was seen in *mdx*. In the young animals as well as in the adults, degenerative changes in the muscle fibres were found in the presence of intact normal-looking nerve terminals (figs 14, 15). Even when the internal structure of the muscle fibre was totally disorganized and necrotic and only remnants of organelles and basal lamina remained, the axonal terminals contained normal-looking mitochondria and synaptic vesicles in apparently normal numbers (fig. 15).

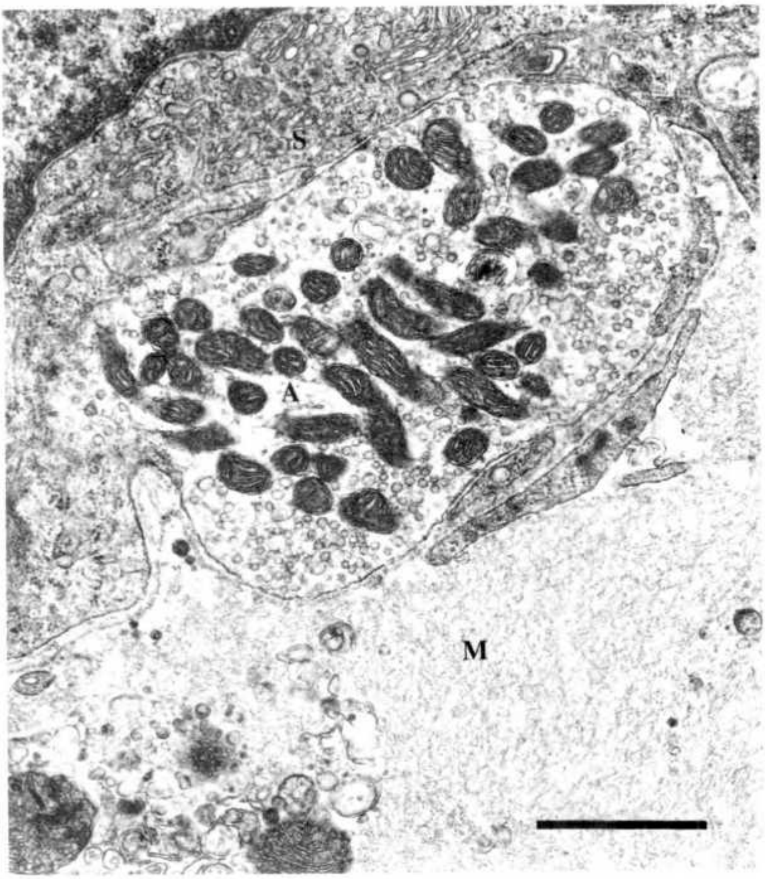


FIG. 15. Motor end-plate on an acutely necrotic muscle fibre (M) in soleus of a 7-weeks *mdx*. The axonal terminal (A) is normal in appearance although the internal structure and plasmalemma of the muscle fibre are disrupted. S = Schwann cell. Bar = 1 μm.

A striking abnormality which was found in end-plates of *mdx* concerned the complexity of the postsynaptic membrane of the muscle fibre. As early as at 4–6 weeks some end-plates already showed a reduction in the number of postsynaptic folds, and those which were present tended to be shallow. It may be that the postsynaptic membrane was already abnormal at an earlier age than 6 weeks but since normally the end-plates are still in process of maturation it was not possible to be certain of this

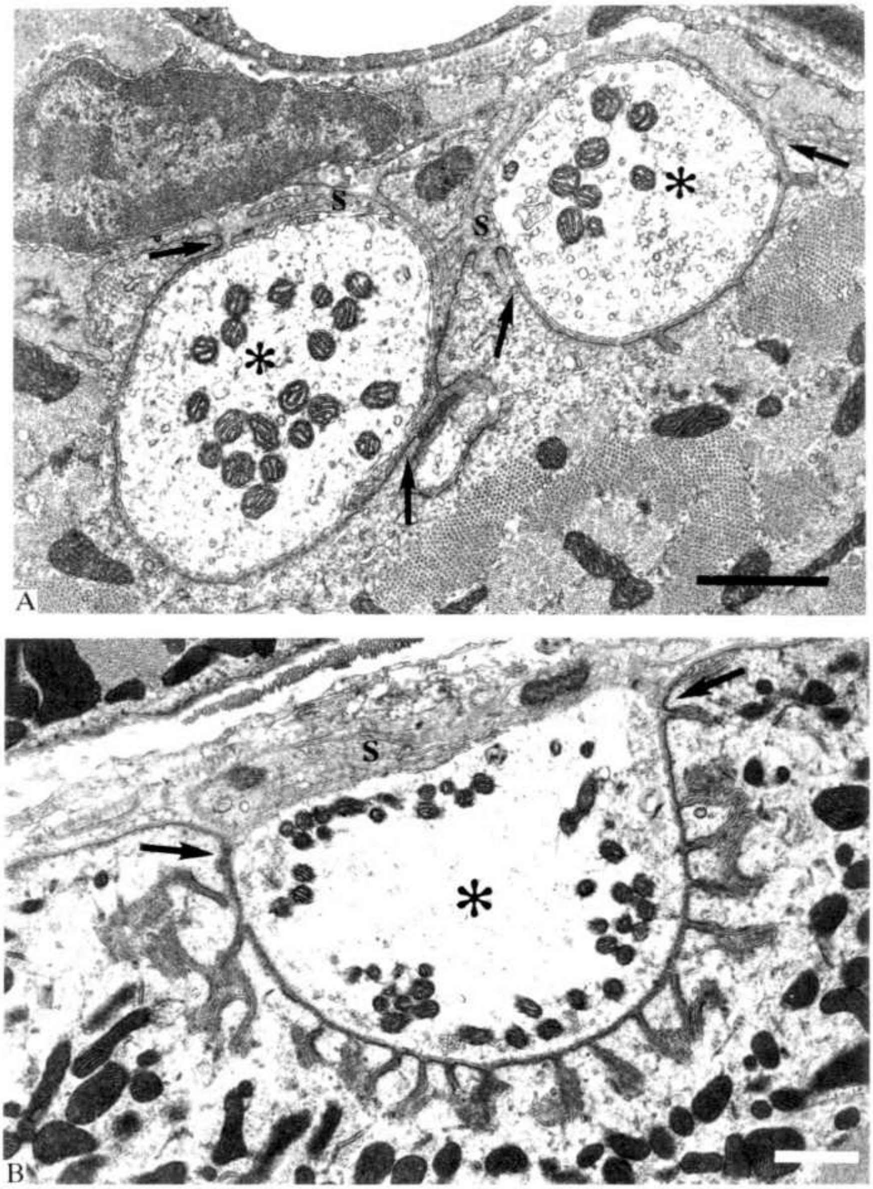


FIG. 16. Motor end-plates in soleus of 6-months *mdx* (A) and normal mouse (B). The axonal terminals (*) are normal but the postsynaptic region of the plasmalemma of the muscle fibre (between arrows) is markedly less infolded in the *mdx* than in the normal. S = Schwann cell. Bars = 1 μm.

point. With increasing age the simplification of the postsynaptic membrane became more obvious and was found in a greater proportion of end-plates. At 6 months (fig. 16) the differences in complexity of postsynaptic infolding between *mdx* and controls was very striking and was analysed morphometrically.

The soleus muscles of 1 *mdx* mouse and 4 controls were cut transversely, and 37 *mdx* end-plates and 72 in the normals, were studied. In most of the muscle fibres of the *mdx* on which the neuromuscular junctions were photographed, there were central nuclei indicating previous degeneration and regeneration. Results are shown in Table 1.

It can be seen that there were no significant differences in size of nerve terminals, vesicle density or presynaptic length. The postsynaptic length (reflecting the number and depth of folds), the postsynaptic area of sarcoplasm, and the ratio between postsynaptic and presynaptic membrane lengths were all markedly reduced, reaching levels of only 50% of normal. Histograms comparing these abnormal postsynaptic parameters in the *mdx* with the control values are shown in fig. 17. In all stages a marked difference in frequency distribution in both groups of animals is present. These observations confirm the impression gained from qualitative microscopy. It should also be stated that occasional end-plates, even on fibres with central nuclei, were normal in appearance.

Spinal Cord and Peripheral Nerves

Spinal cord and ventral roots. The spinal cord was examined at many levels using a variety of neurohistological techniques. The cord was normal in shape and size and the long tracts were well myelinated. The morphology of ventral horn cells was normal at all stages of the disorder. No necrosis, chromatolysis or neuronophagia was observed. Numbers of ventral horn cells seemed to be normal but no counts of these cells were attempted. Instead it was considered that counting the number of myelinated fibres in motor roots would give a reliable indication as to whether or not there had been loss of ventral horn cells. To this end, the motor root L4 was selected as being the largest tributary of the sciatic nerve and examined in the electron

TABLE 1. MORPHOMETRIC ANALYSIS OF NEUROMUSCULAR JUNCTIONS IN *mdx* AND CONTROL MICE

	mdx	*Control*
No. of n-m junctions	37	72
Presynaptic area (μm^2)	6.4 ± 5.9*	7.8 ± 6.1
Postsynaptic area (μm^2)	2.1 ± 1.5**	4.2 ± 2.5
Presynaptic mitochondrial area (μm^2)	0.8 ± 0.9	1.0 ± 1.1
Presynaptic length (μm)	5.7 ± 2.5	6.3 ± 3.2
Postsynaptic length (μm)	10.0 ± 6.1**	21.3 ± 11.3
No. of vesicles	374 ± 280	470 ± 338
Area of nerve terminal occupied by mitochondria (%)	13.4 ± 7.4	11.6 ± 7.5
Post/presynaptic length	1.7 ± 0.7**	3.5 ± 1.4
Vesicle density ($/\mu m^2$)	66 ± 30	75 ± 82
Postsynaptic length/area	5.4 ± 1.8	5.3 ± 1.0

* Mean ± SD; ** $P < 0.001$ (Mann-Whitney test).

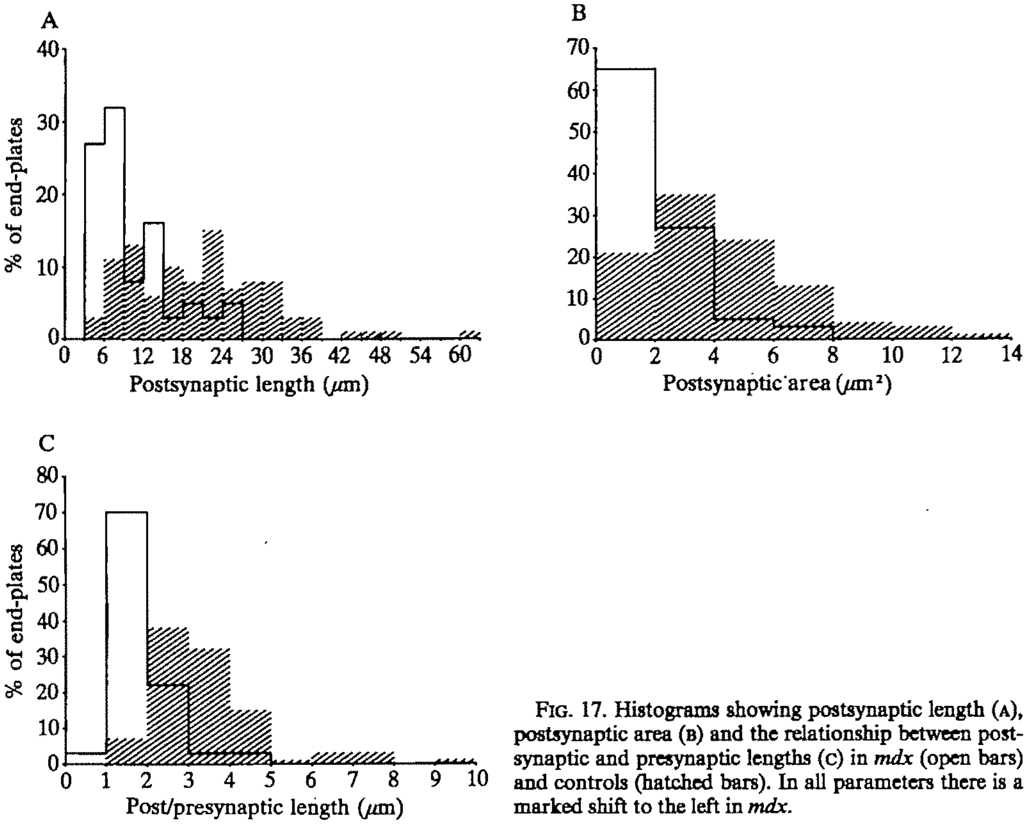


FIG. 17. Histograms showing postsynaptic length (A), postsynaptic area (B) and the relationship between postsynaptic and presynaptic lengths (C) in *mdx* (open bars) and controls (hatched bars). In all parameters there is a marked shift to the left in *mdx*.

microscope. The morphology of axons and their myelin sheaths was normal. There were no hypomyelinated or amyelinated fibres, no wallerian-type degeneration and no evidence of demyelination or remyelination. The total numbers of fibres counted in L4 motor root in 1 *mdx* and 1 control mouse at each of 5 different ages are shown in Table 2. The findings indicate that the number of both myelinated and unmyelinated

TABLE 2. NUMBER OF MYELINATED (MF) AND UNMYELINATED (UF) FIBRES IN L4 MOTOR ROOT

	mdx mouse		*Controls*	
Age (days)	*MF*	*UF*	*MF*	*UF*
14	973	16	816	32
25	881	16	736	28
46	1198	21	1323	19
75	1292	37	1078	0
180	1157	0	1231	10
(x̄ ± SD)	1100 ± 169	18 ± 13	1037 ± 255	18 ± 13

Paired t test $P > 0.1$.

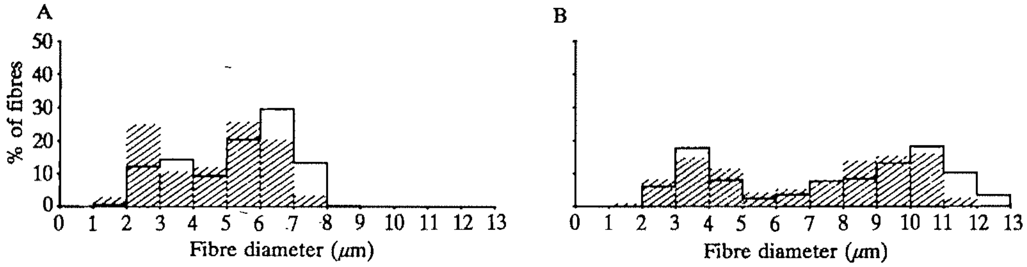


FIG. 18. Histograms showing frequency distribution of myelinated fibre diameters in L4 motor root of *mdx* (open bars) and controls (hatched bars) aged 25 (A) and 75 days (B). At least 400 fibres were measured in each mouse. No significant differences are apparent between the affected and normal animals.

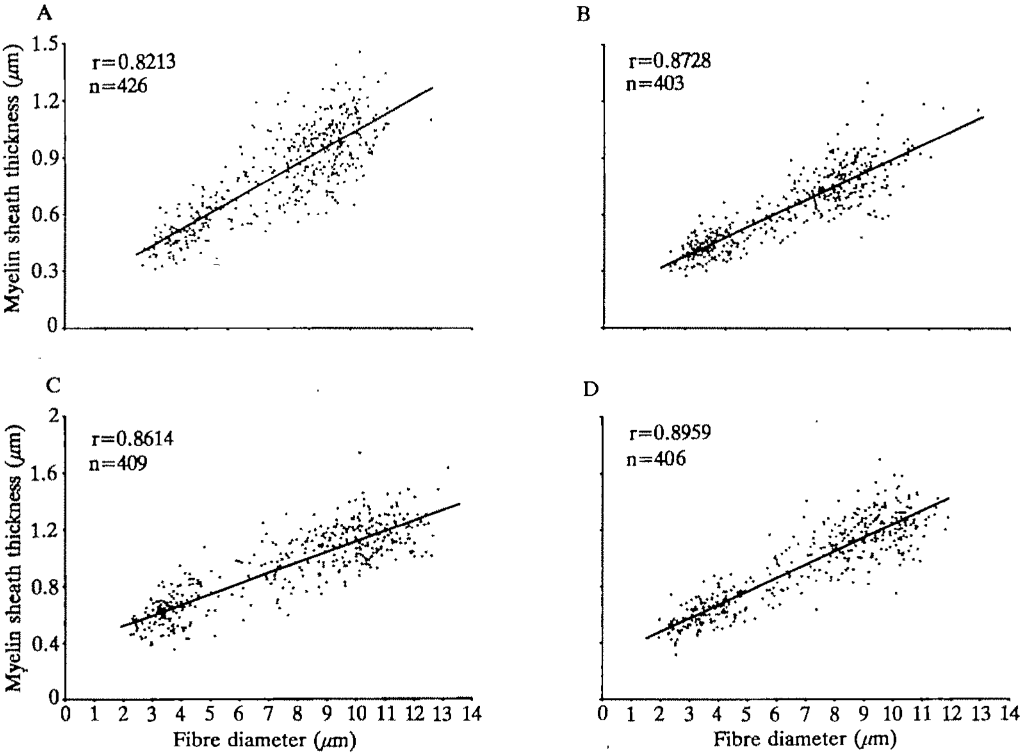


FIG. 19. Scattergrams showing the relationship between myelin sheath thickness and fibre diameter in L4 motor root in *mdx* (A, C) and controls (B, D) aged 25 (A, B) and 75 days (C, D). The slope of regression lines is similar in affected and control animals indicating that myelin sheaths are of appropriate thickness.

fibres were comparable in *mdx* and controls at all the ages studied and that there was no loss of motor fibres with the progression of the disease.

Further morphometric studies of motor fibres were carried out to exclude subtle abnormalities of fibre size and myelin sheath thickness which could contribute to the pathogenesis of the muscle disorder. The fibre size distribution of L4 motor root in

TABLE 3. NUMBER OF MYELINATED (MF) AND UNMYELINATED (UF) FIBRES IN TIBIAL NERVE

	mdx mouse		*Controls*	
Age (days)	*MF*	*UF*	*MF*	*UF*
14	1156	3514	1247	3819
25	1635	4151	1366	2731
46	1600	5300	1463	4429
75	1377	3285	1525	3117
180	1454	4027	1488	3933
($\bar{x} \pm$ SD)	1444 ± 181	4055 ± 781	1417 ± 112	3606 ± 677

Paired t test $P > 0.1$.

mdx and control mice at 25 and 75 days of age is shown in fig. 18. There was no apparent difference between the *mdx* and the normal and the expected bimodal distribution was apparent in both normal and *mdx*. The relationship between fibre diameter and myelin sheath thickness was also found to be normal (fig. 19), further emphasizing the absence of significant pathology in the roots.

Tibial nerve. This nerve was examined in the same animals and with the same methods as already described for the motor roots. Results are shown in Table 3 and figs 20–21. Numbers of fibres, both myelinated and unmyelinated, fibre size distribution and myelin sheath thickness were all comparable to the normal.

Single nerve fibres were teased from peripheral nerves of 1 *mdx* at 75 days of age and 1 control. This was done in order to detect evidence of demyelination and remyelination. Internodal length was found to be directly proportional to fibre diameter in the *mdx*, as in the normal (fig. 22).

Thus the morphological techniques employed revealed no pathological changes in the central or peripheral nervous systems of the *mdx* mouse.

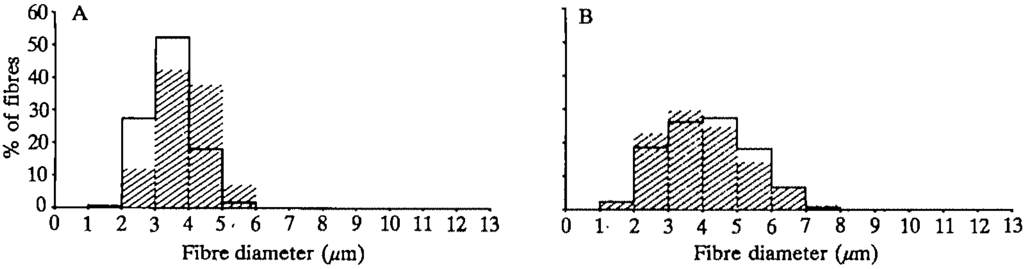


FIG. 20. Diameter frequency distribution of myelinated fibres in tibial nerves of *mdx* (open bars) and controls (hatched bars). No differences were found at any ages studied (more than 400 fibres measured in each nerve). A, 25 days; B, 75 days.

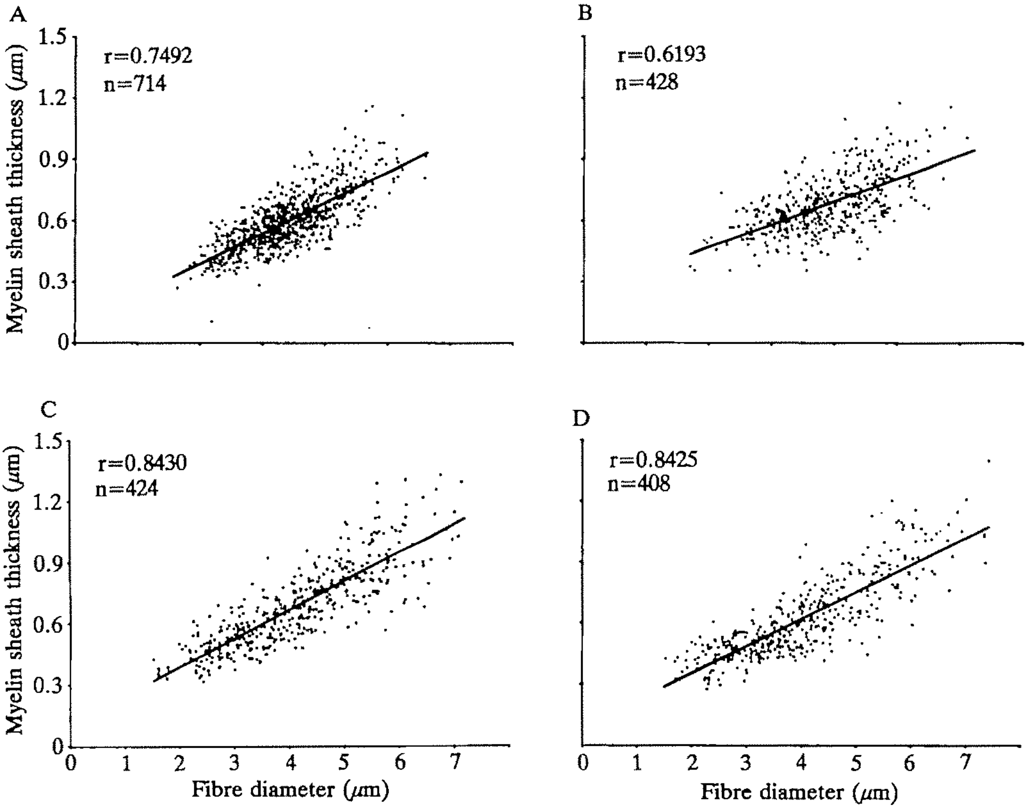


FIG. 21. Relationship between fibre diameter and myelin sheath thickness in tibial nerve of *mdx* (A, C) and control (B, D) mice. A, B, 25 days; C, D, 75 days. The results are very similar as shown by the slopes of the regression lines and coefficients of correlation (r).

DISCUSSION

In the study of neurological mutants in small laboratory animals it is possible to follow the evolution of a disease from its earliest manifestations through to its full expression. This possibility together with the availability of numerous animals, allows the investigator to employ a wide range of techniques and to sample many regions of the nervous system and many different muscles. By these means it is possible to gain an accurate idea of how the disease starts, which are the primary sites of pathology and which are the secondary changes representing healing, regeneration or reaction. Careful pathological examination is needed before the disease process in a new mutant can be correctly identified. The present study of the *mdx* mouse was done using a wide range of morphological techniques to try to put the pathology on a firm basis.

Of the neurological mutants with known pathology in peripheral nerve or muscle, most show obvious behavioural abnormalities such as weakness, incoordination,

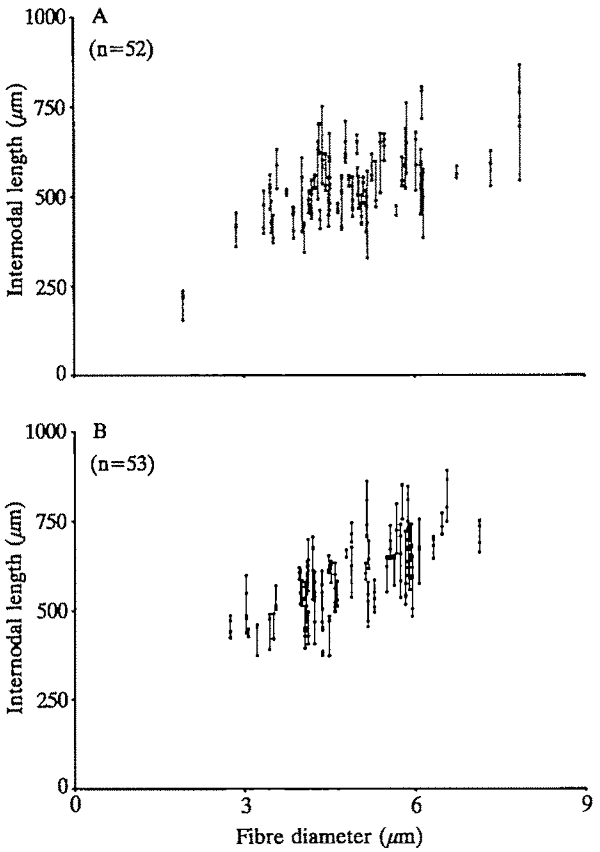


FIG. 22. Graphs showing relationship of internodal length to fibre diameter in teased single fibres of tibial nerve at 75 days of age. Consecutive internodes of a given fibre are plotted along a single vertical line. The normal variation in the lengths of internodes along some fibres and a good linear correlation between internodal length and fibre diameter in control (A) are also present in *mdx* (B).

ataxia or seizure-like disturbances. They may be classified, based on the structures predominantly affected as follows.

1. Those with primary neuronal or axonal pathology. These include *wobbler* (Duchen *et al.*, 1968; Andrews, 1975), *Sprawling* (Duchen, 1975; Duchen and Scaravilli, 1977) and *dystonia musculorum* (Duchen *et al.*, 1964).

2. Mutants with abnormalities of the myelin sheath of peripheral nerve. These include *Trembler* (Falconer, 1951; Ayers and Anderson, 1973), *quaking* (Sidman *et al.*, 1964; Samorajski *et al.*, 1970) and *twitcher* (Duchen *et al.*, 1980). *Dystrophia muscularis* (Michelson *et al.*, 1955) also has an abnormality of myelination (Bradley and Jenkison, 1973, 1975; Biscoe *et al.*, 1974) in addition to many other defects both in muscle and other systems.

3. Some other mutants have been said to show predominantly muscle pathology but have not been extensively studied. These include *myodystrophy* (Lane *et al.*, 1976), and *muscular dysgenesis* (Pai, 1965*a*, *b*; Banker, 1977).

4. Disorders which affect neuromuscular transmission or the motor end-plate. These include *med* (Duchen, 1970; Duchen and Stefani, 1971), although recent work suggests an abnormality in peripheral nerves (Rieger *et al.*, 1984), and *paralysé* (Duchen *et al.*, 1983).

In most of the mutants which have been listed above, skeletal muscle is only secondarily involved, as exemplified by muscle changes in *Trembler* (Gale *et al.*, 1982). The *mdx* mouse, however, is unlike any of these mutants in that there appears to be a total absence of structural pathology in either central or peripheral nervous systems in spite of a severe and extensive muscle disorder. Furthermore the virtual absence of clinical disabilities strengthens the view that peripheral nerve function is probably normal.

Tanabe *et al.* (1986) and Karpati *et al.* (1986) reported that the disorder in the *mdx* mutant mouse begins at about 20 days of age and Dangain and Vrbova (1984) concluded that the muscle changes were the result of a widespread single episode of degeneration occurring at 3–4 weeks followed by regeneration. These reports were based on the study of a few muscles by light microscopy. In the present study it was found that Z-line streaming was present in limb muscles already by the first postnatal day and necrosis was apparent in many fibres of the cranial and axial musculature by 5 days. Furthermore fibre necrosis, as well as regeneration, was observed in muscles of animals as old as one year.

The main features of the pathology of the skeletal muscles in *mdx* were necrosis, regeneration and the persistence of central nuclei. None of these is in itself specific in any way, since these changes are found in a variety of muscle pathologies, both naturally occurring in man and animals and in experimentally induced myopathies (reviewed by Cullen and Mastaglia, 1982; Harriman, 1984). The earliest evidence of pathology in the *mdx* was the disorganization, or 'streaming', of the Z-lines. Although the pathogenesis of Z-line streaming is still uncertain, it has been observed in several other conditions including Duchenne muscular dystrophy (Milhorat *et al.*, 1966), myotonic dystrophy (Casanova and Jerusalem, 1979), in denervated muscle (Miledi and Slater, 1969) and in mutants *muscular dysgenesis* (Platzer, 1979), *Trembler* (Gale *et al.*, 1982) and *dystrophia muscularis* (Platzer and Powell, 1975). It is not certain that in all these conditions Z-line streaming progresses to muscle disorganization and necrosis. Certainly in *Trembler*, muscle necrosis is not a feature. In denervating diseases, muscle fibre necrosis may be found but usually only in very chronic processes in which denervation has been present for a long time. In *mdx* it seems likely that the Z-line streaming progresses to involve more sarcomeres and more myofibrils until the internal stability of the contractile apparatus is undermined and it becomes totally disorganized. This may also happen in some human myopathies but these are never seen at a stage as early as is possible in the animal.

Regeneration of muscle after injury takes a similar form, whatever the cause of fibre necrosis. Debris is removed by macrophages from the sarcolemmal tubes. Proliferation of satellite cells with the formation and subsequent fusion of myoblasts proceeds until the fibre is reconstituted, leaving the presence of central nuclei as an indicator of previous damage. The capacity for regeneration in *mdx* seems to be unimpaired and may explain the lack of muscle weakness and the normal life span. In contrast, in Duchenne muscular dystrophy, regeneration, as assessed by basophilia and large nuclei in small fibres, is seen in the early stages of disease but is less conspicuous when muscle pathology is more advanced (*see* Schmalbruch, 1982). Other features distinguishing the pathology of *mdx* from that of Duchenne dystrophy include the internal nuclei, which are less numerous in the human disease; lymphocytic infiltrations which are absent in *mdx* but may be found in young Duchenne patients; the almost total replacement of some muscles by fat and fibrous tissue in the human but not at all in the mouse; and the absence of involvement of the heart in *mdx*. Therefore, although in both disorders there is a gene defect in comparable regions of the X-chromosome (Bulfield *et al.*, 1984), its phenotypic expression is clearly different in the mouse compared with man.

Although all the morphological studies of the roots and peripheral nerves of *mdx* have shown them to be within normal limits, the neuromuscular junction was the site of significant abnormality. The simplification of the postsynaptic membrane, that is, the reduction in the complexity, number and depth of folds, seems to be secondary to the necrosis and regeneration of the muscle fibres as has been found after the local injection of myotoxins (Duchen *et al.*, 1974) and the local anaesthetic bupivacaine (Jirmanová, 1975). In Duchenne dystrophy Engel *et al.* (1975) and Harriman (1976) have also observed a similar reduction in the complexity of the postsynaptic membrane, but since in this condition it seems likely that regeneration of muscle is less effective than in *mdx*, the significance of the changes in the neuromuscular junction remains in doubt.

Some degree of postsynaptic specialization is found at most synapses, in both the central and peripheral nervous systems. They may be associated with the concentration of receptors at these sites. The *mdx* muscle fibres should be of interest for physiological study since they provide the opportunity for examining the effects of the loss of postsynaptic differentiation on the events and efficacy of neuromuscular transmission which may have a bearing on muscle function in the human dystrophies.

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A QUANTITATIVE HISTOLOGICAL STUDY OF THE CEREBELLAR VERMIS IN ALCOHOLIC PATIENTS

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SUMMARY

A quantitative histological study was made of the cerebellar vermis in 10 male alcoholic and 8 age-matched control cases. The mean Purkinje cell loss was 21% in the alcoholic group. The small rostral and caudal lobes were most severely affected. The mean Purkinje cell density per unit length of foliae showed similar changes. Histological measurements of the area of the molecular, granular and medullary layers of the cerebellar vermis showed that the molecular layer varied in the degree of shrinkage between lobes (from 11 to 39%) while the granular layer showed a consistent shrinkage (9 to 10%). The molecular layer appears to be the most vulnerable region in chronic alcoholics. Brains taken from patients with Wernicke's encephalopathy had particularly low Purkinje cell counts and a large pericerebral space. Nutritional deficiency would seem to be an important factor in the causation of the observed neuropathology, with liver disease playing a lesser role. Evidence that repeated alcohol withdrawal can lead to further brain disturbances is reviewed.

INTRODUCTION

A common clinical syndrome seen in chronic alcoholic patients is ataxia of gait and of the limbs, particularly the legs. In a group of 9 alcoholic subjects, Victor *et al.* (1971) noted that 6 had ataxia and at postmortem all were found to have lesions in the superior vermis, whereas the remaining 3 without ataxia showed no sign of cerebellar lesions. These authors concluded that the chronic ataxia of stance and gait could be related to lesions in the superior vermis, regardless of a peripheral neuropathy which may also contribute. Computerized tomographic (CT) scans have revealed shrinkage of the cerebellar hemispheres and vermis in chronic alcoholics (Haubek and Lee, 1979; Koller *et al.* 1981). These radiological changes are supported by the postmortem findings of Victor and Ferrendelli (1970) and Harper (1982) which show reduced size of some cerebellar lobes. It is not clear, however, how much of this tissue shrinkage is due to irreversible nerve cell loss, and how much relates to reversible retraction of the neuropil (dendrites, axons and connecting synapses), reduced extracellular space, reduced white matter volume

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(Harper *et al.*, 1985*b*) or changes in tissue water content (Smith *et al.*, 1985; Harper *et al.*, 1985*a*).

Human postmortem studies of alcohol-related brain damage, such as that of Courville (1966), were based on a subjective assessment of histological preparations of various brain regions, but were not accompanied by objective observations with statistical comparisons with appropriate control material. Studies of cell loss in the cerebellum are inconsistent; thus in the study by Neubuerger (1957) of 42 alcoholic brains and 5 controls, the main finding was granule cell loss in the cerebellum. On the other hand, loss of Purkinje cells was the predominant feature described by Courville (1966), and Lynch (1960) reported a 20–35% loss of Purkinje cells, but did not give quantitative methodological details. Based on autopsy case reports of 7 alcoholics (no controls), Allsop and Turner (1966) concluded that granule cell loss was the earliest histological change followed by Purkinje cell degeneration in chronic alcoholism.

The proportion of white matter in the cerebral hemispheres has been shown to be a sensitive indicator of difference between alcoholic and control brains (Harper *et al.*, 1985*b*). Additionally, in nonalcoholic disorders, the ratio of the molecular to granular layers has been found to change, and this finding is interpreted by Friede (1963) as an indicator of oedema in the human cerebellum. Thus area measurements in histological sections can serve as a valuable aid in the postmortem assessment of various pathological disorders in conjunction with estimates of change in cell populations. The present paper reports a quantitative histological comparison of the cerebellar vermis in alcoholic and age-matched control subjects.

MATERIALS AND METHODS

The material used in this study was largely obtained from forensic autopsies. Only male patients were included in the study. Classification of cases into control and alcoholic groups was based on compilation of clinical and pathological data. The data included clinical notes available from the teaching hospitals of Perth as a result of previous admissions, detailed questionnaires on alcohol intake and nutritional state provided by relatives of the subjects, reports concerning circumstances of death, and a complete necropsy with microscopic examination of tissues including the brain. In many cases liver function studies were available, and in 5 cases CT scans had been performed. Patients with a history or pathological evidence of neurological diseases other than those associated with alcoholism were excluded. Any patient with macroscopic evidence of head injury was excluded from the study, as were control subjects in whom there was a history of moderate alcohol intake. Both groups of brains were age-matched, and clinical details appear in Table 1. The control and alcoholic cases were number coded and the code broken only after completion of the quantitative studies.

Brains were removed from the skull between 18 and 105 h after death. After weighing the whole brain, the cerebellum and brainstem were removed, weighed, and fixed by immersion in 10% formalin for 2–3 weeks. After fixation, the brainstem was removed and the cerebellum divided into two halves by a midsagittal cut. A parasagittal cut was made about 1 cm to the left of the midline to produce a slab of tissue containing the vermis. Using tracing paper placed against the midline surface of the vermis the folial outline was recorded so that the area of the cut surface could be measured using a

Zeiss MOP-1 image analyser. The slab was then embedded in paraffin wax using standard Histokinette procedures.

Sections each 30 μm thick were taken from the medial (vermial) surface of the slabs and stained with 0.05% toluidine blue in sodium phosphate buffer, pH 7.4, for 10 min, and rinsed in fresh buffer for 20 min. The sections were then cleared in xylol and mounted on large glass slides in DPX.

The surface area of the histological section was measured. Comparison of this measurement with that of the previously measured fixed tissue area allows an estimate to be made of area shrinkage. Additionally, the linear distance between the apex of lobe I and the apex of lobe VI (fig. 1) was measured before and after embedding so that an estimate of linear shrinkage was also available. For anatomical descriptive purposes, the nomenclature which recognizes ten lobes of the human cerebellar vermis was most appropriate (Angevine *et al.*, 1961; Voogd, 1967; Noback, 1981). Fig. 1 illustrates these ten vermial regions in roman numerals.

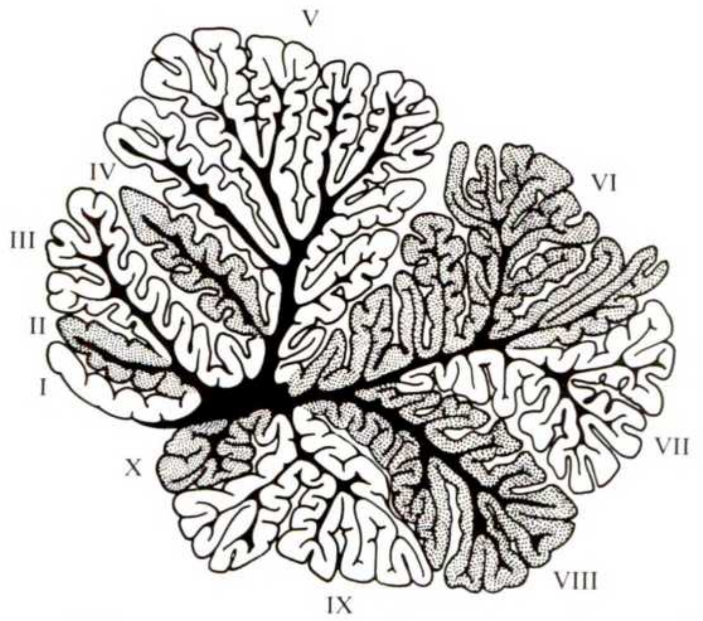

FIG. 1. The appearance of a midsagittal section of human cerebellar vermis. White matter (medullary layer) is indicated in black. Grey matter (molecular and granular layers) is indicated in white or speckled. Even-numbered lobes are speckled. The anterior vermis is located to the left.

Purkinje cell counting was performed at × 40 magnification using a hand-held counter. Toluidine blue stains the cytoplasm of Purkinje cells intensely while leaving the surrounding neuropil relatively unstained. The resulting high contrast between the cell and the neuropil permits counting to be performed with ease and confidence. Purkinje cells are so large, rich in cytoplasm and reliably located anatomically, that they are readily identified and cannot be confused with any other cell type (fig. 2). All visible Purkinje cells were counted. From 6 of the brains, four serial sections were prepared for cell counting, and a variation from 0 to 6% was found in the Purkinje cell count between these serial sections within any one brain. In view of this small variation between sections, cell counts were performed from one midsagittal section from each brain.

In addition to determining Purkinje cell populations and densities in each lobe of the cerebellar vermis, the histological areas of the three different types of tissue which constitute the cerebellum were measured: the essentially cell-free molecular layer, the high cell density granular layer and the

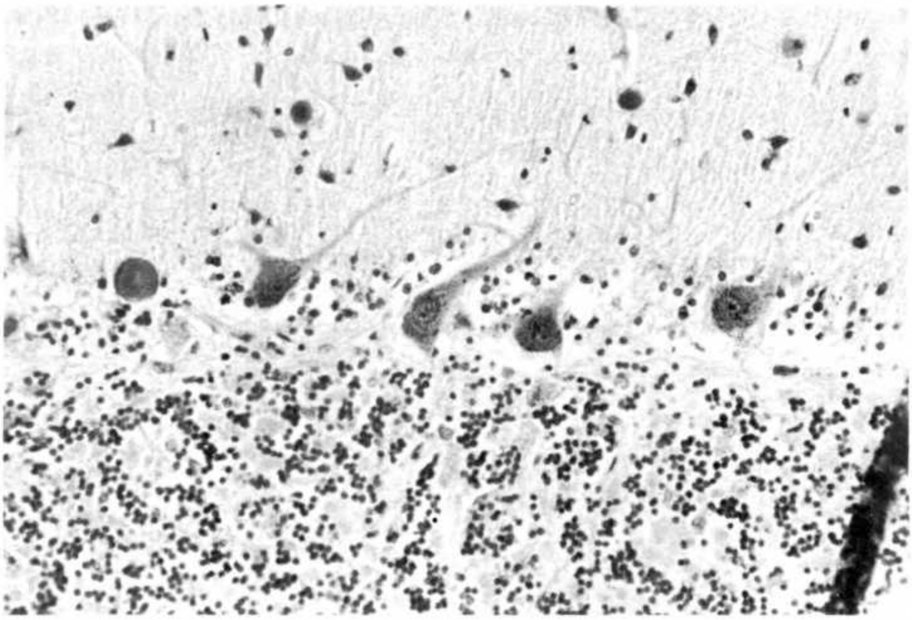

FIG. 2. The appearance of cerebellar Purkinje cells in 10 μm paraffin sections stained with toluidine blue.

axon-filled medullary layer. Length and area measurements were performed using a Leitz Neopromar projection microscope and a Zeiss MOP-1 image analyser. The image cast by the projection microscope was 20 times the size of the histological section, and the image analyser was programmed to incorporate a correction factor so that the recorded value represented the length or area in the paraffin section. Purkinje cell (somata) size was estimated by measuring the circumference of 20 randomly chosen cells from each lobe and then dividing these values by π. Randomness of cell selection was obtained by casual flicks of the microscope stage controls. The average diameter of the Purkinje cells was determined using the method described by Walton (1948).

Students' t test was used for all statistical comparisons.

RESULTS

The age of the alcoholic patients varied from 52 to 69 years (mean 61.2) and the controls varied from 57 to 85 years (mean 68.5). Data on the condition of the liver were available for some of the patients, and these have been listed in Table 1. Mean total brain weight after 2–3 weeks' fixation for the alcoholic group was 1330 ± 112 g (mean ± SD) which is 6% ($P < 0.07$) less than the control group value of 1418 ± 109 g. The weight of the cerebellum (with brainstem attached) was 174 ± 16.6 g for the alcoholic group compared with 178 ± 12.8 g for the control group (Table 2), which is only 2% less (n.s.).

Area Measurements

The mean total cross-sectional area of the cerebellar vermis of fixed alcoholic brains before paraffin embedding (937 ± 164 mm^2) was not significantly different

TABLE 1. CLINICAL DETAILS

Case	*Age (yrs)*	*Postmortem delay (h)**	*Neuropathological findings*	*Liver condition*	*Liver function tests*	*Drinking history available*
A1	54	25	Severe vermis and lateral cerebellar hemisphere atrophy. Wernicke's encephalopathy.	Cirrhosis	—	No
A2	69	36	Slight ventricular dilatation. Hepatic encephalopathy. Slight vermis atrophy.	Cirrhosis	—	No
A3	62	26	Slight ventricular dilatation.	Normal	—	Yes
A4	52	22	Mild cerebellar vermis atrophy.	Cirrhosis	Abnormal albumen, abnormal bilirubin	Yes
A5	59	21	Mild cerebellar atrophy. Lacunes in basal ganglia.	Cirrhosis	Normal albumen, abnormal bilirubin	Yes
A6	68	37	Old traumatic lesions of both occipital cortices. Lacunes in basal ganglia.	Normal	Abnormal albumen	No
A7	61	96	Chronic Wernicke's encephalopathy. Vermis atrophy.	Cirrhosis	—	No
A8	66	35	Old haemorrhage in interventricular septum. Hepatic encephalopathy. Slight vermis atrophy.	Cirrhosis	—	No
A9	59	53	Frontal atrophy, ventricular dilatation, mild vermis atrophy. Chronic Wernicke's encephalopathy.	Fatty liver	—	No
A10	62	53	Microinfarcts in parietal white matter and basis pontis. Gliosis in medial dorsal nucleus of thalamus.	Cirrhosis	—	No
C1	69	46	No abnormalities.	Normal	—	Yes
C2	85	33	Minute left occipital lobe infarction.	Normal	—	Yes
C3	74	28	Mild cerebral atrophy. Pontine haemorrhage.	Postinfectious fibrosis	Abnormal albumen, abnormal bilirubin	Yes
C4	64	40	No abnormalities.	Normal	Normal albumen, normal bilirubin	Yes
C5	57	18	No abnormalities.	Postop. biliary obstruction	Normal albumen, abnormal bilirubin	Yes
C6	75	30	Moderate cerebral atrophy.	Normal	—	Yes
C7	60	105	No abnormalities.	Fatty liver	—	Yes
C8	64	100	No abnormalities.	Normal	—	Yes

* Delay between death and brain fixation.

(6% less) from the equivalent value for control brains (998 ± 80 mm^2). The mean shrinkage in area in histological sections due to paraffin embedding in the alcohol group ($23 \pm 8\%$ less than cross-sectional area of fixed brain) was the same as that for control brains ($23 \pm 4\%$). Thus in the two groups of cases (controls and alcoholics) the brain tissue is no more or less susceptible to tissue shrinkage during the paraffin embedding process.

For histological area measurements, three lobes of the vermis were selected: the rostrally located lobe IV, the mid-rostrocaudally located lobe VII and the caudally located lobe X. These lobes are portions of the superior vermis, midvermis and inferior vermis respectively. The results of these measurements are listed in Tables 3 and 4. Lobe IV (superior vermis) in the alcoholic group showd a 26% ($P < 0.05$) reduction in total histological section area with lobes VII (8%) and X (10%) showing the same trend but the differences not being statistically significant. Lobe IV also showed a 26% ($P < 0.01$) reduction in the molecular/granular area ratio in the alcoholic group, this difference being principally attributable to a 39% ($P < 0.01$) decrease in the area of the molecular layer. Although there were no significant differences in any of the measurements made in lobes VII or X, it is the

TABLE 2. QUANTITATIVE RESULTS FOR BRAIN AND CEREBELLAR WEIGHT

Case	*Total fresh brain weight (g)*	*Fresh cerebellar weight (with brainstem attached) (g)*	*Total Purkinje cell count in one histological section*	*Mean Purkinje cell diameter (μm)*
A1	1157	167	1568	46.6
A2	1390	170	5928	46.8
A3	1262	171	8528	42.6
A4	1419	188	5377	45.6
A5	1322	153	4173	45.0
A6	1330	182	5599	45.0
A7	1440	178	4517	46.9
A8	1250	171	3811	45.5
A9	1515	210	4969	44.4
A10	1210	154	5111	42.2
Mean	1330	174	4958	45.1
C1	1487	168	5329	46.6
C2	1279	168	8539	45.3
C3	1333	177	5762	45.1
C4	1479	170	5440	46.1
C5	1505	187	8447	43.9
C6	1320	187	4543	44.4
C7	1585	203	4792	44.0
C8	1359	168	7327	44.3
Mean	1418	178	6272	45.0

molecular layers in these two lobes that again showed the greatest reduction in area in the alcoholic group. The area of the granular layer was also consistently lower (9 and 10%) in the alcoholic group.

In all three lobes studied, there was no significant difference between the two groups in the ratio of grey to white matter (expressed as the sum of the molecular and granular layers divided by the medullary layer), although there was a consistent decrease in the alcoholic group in the three lobes measured.

Cell Counts

There was no significant difference in the diameter of Purkinje cells between the alcoholic (45.1 ± 1.6 μm) and control (45.0 ± 1.0 μm) groups. Therefore, the numbers of cells counted in the histological sections are a reflection of the numbers present in the respective tissues.

Patients with Wernicke's encephalopathy (diagnosed at autopsy) had vermal Purkinje cell counts of 1568, 4517 and 4969 (mean = 3686) per histological section, whereas the mean for non-Wernicke patients was 5504 cells/section (Table 2). Thus patients with Wernicke's encephalopathy appear to have a lower Purkinje cell count per histological section than those with alcoholic cerebellar degeneration.

TABLE 3. HISTOLOGICAL AREA MEASUREMENTS IN THREE LOBES OF THE VERMIS IN ALCOHOLIC AND CONTROL CASES[1]

Measurement	*Control*	*Alcoholic*	*% difference*
Lobe IV			
Molecular layer (mm^2)	27.5 ± 5.1	16.8 ± 7.9	−39[2]
Granular layer (mm^2)	19.2 ± 2.9	17.2 ± 9.2	−10
Medullary layer (mm^2)	10.1 ± 1.7	7.8 ± 3.0	−23
Total area (mm^2)	56.7 ± 9.0	41.9 ± 18.8	−26[3]
Lobe VII			
Molecular layer	13.8 ± 5.5	12.3 ± 8.9	−11
Granular layer	10.9 ± 3.5	9.9 ± 4.0	−9
Medullary layer	4.3 ± 1.5	4.3 ± 3.5	0
Total area	29.0 ± 9.1	26.5 ± 15.4	−8
Lobe X			
Molecular layer	38.3 ± 23.1	33.9 ± 20.0	−11
Granular layer	33.5 ± 16.0	30.0 ± 19.8	−10
Medullary layer	12.4 ± 4.0	11.6 ± 7.1	−6
Total area	84.2 ± 41.3	75.5 ± 47.4	−10

[1] Values (means ± SD) are adjusted for individual brain shrinkage due to paraffin embedding; [2] $P < 0.05$; [3] $P < 0.01$.

TABLE 4. HISTOLOGICAL AREA RATIOS IN THREE LOBES OF THE VERMIS IN ALCOHOLIC AND CONTROL CASES[1]

Ratio	*Control*	*Alcoholic*	*% difference*
Lobe IV			
Molecular/granular	1.43 ± 0.17	1.06 ± 0.33	−26[2]
Molecular + granular/ medullary	4.68 ± 0.61	4.20 ± 1.40	−10
Lobe VI			
Molecular/granular	1.27 ± 0.21	1.24 ± 0.36	+2
Molecular + granular/ medullary	5.79 ± 2.26	5.15 ± 1.14	−11
Lobe X			
Molecular/granular	1.14 ± 0.30	1.13 ± 0.30	−1
Molecular + granular/ medullary	5.74 ± 4.08	5.40 ± 2.55	−6

[1] Values = mean ± SD; [2] $P < 0.01$.

CT scans were made on 5 of the alcoholic patients at various times before death: A2 (6 weeks), A4 (1 day), A7 (18 months), A8 (14 months) and A10 (about 2 years). No focal lesion was present in A4 but cerebral atrophy was observed in A2, A7 and A8. Cerebellar atrophy was evident in A2 and A10, but these two

TABLE 5. PURKINJE CELL COUNTS AND LINEAR DENSITIES FOR THE 10 DIFFERENT CEREBELLAR LOBES IN ALCOHOLIC AND CONTROL CASES[1]

Cerebellar lobe	*Control group*	*Alcoholic group*	*Percentage difference*	*Level of significance*
Purkinje cell counts				
I	40.5 ± 12.3	25.2 ± 23.9	−38	$P < 0.05$
II	123.0 ± 42.9	88.5 ± 55.2	−28	$P < 0.08$
III	315.3 ± 143.5	243.2 ± 137.6	−23	n.s.
IV	343.4 ± 157.9	276.9 ± 166.8	−20	n.s.
V	1622.1 ± 421.2	1349.4 ± 713.2	−17	n.s.
VI	1321.9 ± 374.9	1124.7 ± 642.4	−15	n.s.
VII	652.8 ± 323.5	536.2 ± 249.5	−18	n.s.
VIII	827.5 ± 304.7	713.4 ± 249.2	−14	n.s.
IX	744.8 ± 275.6	416.6 ± 196.6	−44	$P < 0.01$
X	281.3 ± 55.0	184.0 ± 92.0	−35	$P < 0.01$
Total	6272.4 ± 1608.8	4958.1 ± 1761.1	−21	$P < 0.06$
Purkinje cell densities (cells/mm)				
I	5.76 ± 2.78	3.56 ± 2.14	−38	$P < 0.04$
II	6.80 ± 1.39	6.26 ± 4.57	−8	n.s.
III	6.99 ± 1.67	4.82 ± 1.73	−31	$P < 0.01$
IV	8.64 ± 7.20	4.67 ± 2.19	−46	$P < 0.07$
V	6.93 ± 1.27	5.81 ± 3.34	−16	n.s.
VI	7.78 ± 1.77	7.19 ± 4.46	−8	n.s.
VII	6.56 ± 1.39	7.00 ± 2.95	+7	n.s.
VIII	6.44 ± 1.20	6.90 ± 4.17	+7	n.s.
IX	6.57 ± 0.81	5.18 ± 1.77	−21	$P < 0.01$
X	8.65 ± 3.04	8.12 ± 4.07	−6	n.s.
Total	7.11 ± 1.39	5.95 ± 2.49	−16	n.s.

[1] Density values (means ± SD) have been adjusted for shrinkage due to paraffin embedding.

brains did not show a greater Purkinje cell loss than A4, A7 or A8. Thus the degree of tissue shrinkage of the cerebellum revealed by CT scanning cannot be equated unequivocally with Purkinje cell loss.

Amongst both the alcoholic and control groups of brains, there is a large variation in Purkinje cell counts for each of the lobes, which is reflected in the SD values (Table 5). Despite this high variability between individuals, the total Purkinje cell count per histological section (Table 5) was 21% lower in alcoholics relative to controls which is close to statistical significance ($P < 0.06$). When the lobes of the vermis are considered separately, it is clear that it is the smaller sized lobes (lobes I, II, III, IX and X) which have sustained the greatest cell loss. These five lobes in the alcoholic group all have a mean Purkinje cell loss greater than for the total histological section count with three of them reaching statistical significance (Table 5).

When the length of the Purkinje cell line is measured for each lobe of each brain, and this figure then corrected for the linear shrinkage due to paraffin embedding for that particular brain, the linear density of Purkinje cells can be calculated. These values are also listed in Table 5. Note that it is the smaller sized lobes that have sustained the greatest reduction in Purkinje cell density. Lobes VII and VIII each showed a loss (14–18%) of Purkinje cells in the alcoholic group, but this was accompanied by a 7% increase in cell density relative to controls. This difference could be interpreted as an indication that the shrinkage of the neuropil or granular cell layers exceeded the rate of Purkinje cell loss.

DISCUSSION

This is a quantitative neuropathological study of the human cerebellar vermis of an alcoholic and an age/sex-matched control group after fixation. The same fixation procedure was used as employed by Hall *et al.* (1975) in their quantitative study of the normal human cerebellum. Hall *et al.* (1975) concluded 'that the effect of fixation is minimal and it would be safe to work directly from fixed tissue'. They recorded a measurable fall in Purkinje cell counts in histological sections with age, particularly after the sixth decade of life. There was only a slight difference in age beween our alcoholic and control groups, with the control group being 10% older on average. Thus our alcoholic-to-control comparisons listed in Tables 3–5 are, if anything, conservative.

The diagnosis of cerebellar atrophy or Wernicke's encephalopathy in 7 of the brains from the alcoholic group is indicative of the severity of the alcoholic condition of the subjects used in this study. However, we have found only a 2% reduction in mean cerebellar weight and the mean Purkinje cell loss for the most anterior lobe was 38%. Skullerud (1985) found a 6% loss of cerebellar weight in male alcoholics in both the 45–54 and 70–79 year age groups. Moreover, he observed 'complete loss of Purkinje cells over entire folia in the anterior and superior vermis' in those cases which had alcoholic cerebellar atrophy (7/28 alcoholics). In this human study, we have found that the small rostral lobes (I, II, III and IV) and caudal lobes (IX and X) have shown the greatest Purkinje cell loss (20% or more). In animal studies involving alcohol administration in combination with a nutritious diet for 4 to 5 months followed by abstinence for 2 to 4 months, the large mid-rostrocaudally located lobes have shown the greatest Purkinje cell loss in mice (Phillips and Cragg, 1984) and rats (Barnes and Walker, 1979).

The quantitative histological measurements in this study confirm the macroscopic observations of Victor *et al.* (1959) that the small rostral lobes have the greatest reduction of tissue content. Moreover, the molecular layer appears to be the most sensitive of the three tissue components (dendritic, neuronal cell bodies and axon layers) of the cerebellum to the effects of alcoholism. The reductions in the area of the molecular layer in alcoholics were from 11 to 39% less than in the controls. This was dependent on the cerebellar lobe examined. Conversely, the granule cell layer of the cerebellar vermis displayed a consistent 9 to 10% reduction in area in the three lobes studied. Thus areas with a high synaptic content show greater change than those areas of high cellular content. Decreased dendritic arborization has been suggested as a cause of the shrinkage of cerebral hemispheres in CT scans of alcoholics (Carlen *et al.*, 1978). Ferrer *et al.* (1984) has observed reduced dendritic arborization of Purkinje cells (particularly of the rostral lobes) in their Golgi study of 4 alcoholic patients. Relative to 6 control patients, they found the length of the Purkinje dendrites to be reduced by 12% at the base of sulci and 32% at the tips of the lobes. In an experimental model, Tavares *et al.* (1983) recorded a 41% decrease in Purkinje cell dendritic branching in Golgi stained cerebellar sections from rats after 6 months of alcohol consumption.

The large, mid-rostrocaudally located lobes (V, VI, VII and VIII) each showed less Purkinje cell loss than that for the total of all lobes. It is therefore not surprising that these four lobes showed the smallest change in Purkinje cell density. The greatest Purkinje cell losses were recorded in the small lobes of the vermis located both rostrally and caudally. Such degeneration in the rostral lobes is similar to that seen in nonalcoholic nutritional deficiency, and this similarity, combined with the knowledge that alcoholics are often malnourished, led Victor and Ferrendelli (1970) to state that 'alcoholic cerebellar degeneration is in all likelihood due to nutritional deficiency'. Wernicke's encephalopathy is caused by vitamin B_1 (thiamine) deficiency (Victor, 1979), and Victor *et al.* (1971) believed 'the cerebellar lesions of Wernicke's encephalopathy and of alcoholic cerebellar degeneration represent the same disease process'.

The Purkinje cell count data presented in this study suggest, however, that patients with Wernicke's encephalopathy have more severe neuronal loss than alcoholic patients without this condition. This can perhaps be related to the severity of brain shrinkage. The pericerebral space (percentage difference between intracranial and brain volumes) was measured in a proportion of these cases (A1, A3, A4, A5, C2, C5 and C6) using a recently described technique (Harper *et al.*, 1984). The brain with the lowest Purkinje cell count (A1) had the highest pericerebral space (20.1%) which reflects severe brain shrinkage. In a previous study, Harper and Kril (1985) showed that alcoholic patients with Wernicke's encephalopathy have a mean pericerebral space of 14.7% ± 5.8% ($n = 10$) while for non-Wernicke alcoholics the pericerebral space was 11.3% ± 5.2% ($n = 15$). Nonalcoholic controls had a value of 8.3% ± 3.3% ($n = 44$).

It is conceivable that the changes in the brain may be a secondary effect of associated liver disease (cirrhosis). There is neuroradiological (CT) evidence of brain shrinkage in alcoholics with cirrhosis (Fox *et al.*, 1976). Subsequent studies, however, on alcoholics in which CT scans, liver biopsies and psychometric tests have been done have been inconsistent, in that Lee and her colleagues (1979) showed that there was no correlation between liver disease and cortical atrophy, whereas Acker *et al.* (1982) showed a significant correlation. Thus it is possible that the metabolic disorders associated with liver dysfunction could be a contributory factor additional to malnutrition in the causation of brain damage in alcoholism and might explain the great variability in the histological findings in this study. Other quantitative studies of brain shrinkage by the authors suggest that in the alcoholic cases studied, those with cirrhosis of the liver have only marginally more severe shrinkage than do those without this complication (Harper and Kril, 1986).

Brain shrinkage has been well documented in other nutritional deficiency states, anorexia nervosa in particular (Heinz *et al.*, 1977). This reverts towards normality once a normal diet is recommenced. Considerable fluctuations can occur in liver function dependent upon diet and the amount of ethanol being consumed. Thus both these factors (diet and liver function) are potentially correctable to some degree. Since dendrites, axons and their connecting synapses can regrow in the adult mammalian central nervous system (Sumner and Watson, 1971), it is possible that the brain may undergo some repair in the abstinent alcoholic patient in the long term. This idea has been put forward as a possible explanation for the reversibility of brain shrinkage in abstinent alcoholic patients as seen in CT scans (Carlen *et al.*, 1978). Experimental studies with mice maintained on a nutritionally complete diet do indeed show signs of synaptic replacement in the molecular layer of the cerebellum after 4 months of withdrawal from a 4-month period on an alcoholic intake (Phillips, 1985). Clinical tests of muscular coordination indicate reduced truncal ataxia in patients that have been abstinent for 3 to 40 months (Diener *et al.*, 1984).

Chronic alcoholic patients frequently follow a course of repeated binge drinking, each ending with a period of either voluntary or involuntary abstinence or withdrawal (Babor *et al.*, 1980). The frequency and severity of these withdrawal phases is often not recorded in the medical history of the patient (because it is either impossible for the clinician to keep track of the patient, or because the patient is not fully truthful or accurate in describing his experiences). Yet clinical studies show that the early period of withdrawal involves significant metabolic disturbances to the brain: CSF acidosis (Carlen *et al.*, 1980), cerebral overhydration (Besson *et al.*, 1981), CSF hypomagnesaemia (Meyer and Urban, 1977) and hypokalaemia (Wadstein and Skude, 1978) have been recorded in alcoholics during the early stages of withdrawal. Moreover, the level of synapse-specific protein in the CSF of alcoholic patients experiencing delirium tremens has been shown to be elevated by 90% relative to those levels in the same patients when admitted to hospital while still intoxicated (Jørgensen *et al.*, 1980). This result has been reproduced in an experimental animal model (Hemmingsen and Jørgensen, 1980). These changes may reflect increased synaptic breakdown during withdrawal, and biochemical studies in rats indicate that there is no parallel increase in cortical and thalamic protein synthesis during the early stages of the withdrawal condition when seizures and hyperactive behaviour is at a peak (Tewari *et al.*, 1977; Peters and Steele, 1982).

CT scan studies have been performed on alcoholic patients in order to observe changes in brain shrinkage following abstinence (Carlen *et al.*, 1978; Ron *et al.*, 1982). However, these studies emphasized the changes in the cerebral hemispheres and scant attention was given to changes in the cerebellum during abstinence. Thus there is little information on the gross anatomical changes of the human cerebellum following abstinence.

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HEREDITARY GENERALIZED AMYLOIDOSIS WITH POLYNEUROPATHY

CLINICOPATHOLOGICAL STUDY OF 65 JAPANESE PATIENTS

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SUMMARY

A clinicopathological study was made on 65 patients from a small area of Nagano Prefecture, Japan, with hereditary generalized amyloidosis with polyneuropathy to clarify the clinical variety of the disease. Forty-five patients from Ogawa village showed similar clinical features. The age of onset ranged widely from 16 to 62 years. The main neurological manifestations were polyneuropathy starting in the legs and autonomic dysfunction. Lower cranial nerves were also affected in the advanced stages. Severe cardiac and renal involvement was uncommon. All these clinical features are consistent with type I familial amyloid polyneuropathy (FAP).

The remaining 20 patients from five unrelated kinships showed unique clinical pictures. Two families from Ogawa village had type I FAP, but 4 out of the 5 affected patients showed marked nephropathy with heavy proteinuria from an early stage. Of the three other families, one, with 10 patients, was notable for the involvement of the central nervous system. Most of the patients showed cerebellar ataxia and pyramidal tract signs in addition to a sensorimotor and autonomic peripheral neuropathy. Another family had 2 siblings who had severe amyloid heart disease from the onset and developed polyneuropathy with autonomic features at an advanced stage. In the third family, onset occurred in the sixth decade in all 3 patients and the course was mild in 2, although the clinical features were those of typical type I FAP. Immunohistochemical study revealed that the amyloid fibril proteins in the patients with all four unusual clinical phenotypes were related to plasma prealbumin.

The most common form of hereditary generalized amyloidosis in Japan is type I FAP, but the disease shows considerable variety in the age of onset and involves more systemic organs than previously recognized. The newly recognized clinical forms of hereditary generalized amyloidosis with severe amyloid heart disease or central nervous dysfunction indicate clinical heterogeneity of hereditary amyloidosis with polyneuropathy.

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INTRODUCTION

Hereditary amyloidosis is a heterogeneous group of familial diseases that has in common the systemic or localized accumulation of amyloid fibrils (Glenner *et al.*, 1978). In those variants where there is predominant involvement of peripheral nerves from the onset, the term familial amyloid polyneuropathy (FAP) is generally used. FAP was first described by Andrade in Portugal (1952). The main conclusions of his paper were (1) the disorder is inherited as an autosomal dominant trait with equal sex distribution; (2) the age of onset is 25 to 35 years, leading to death from cachexia in ten to twelve years; (3) polyneuropathy with sensory dissociation began in the legs and progressed in an ascending fashion; (4) manifestations of autonomic dysfunction invariably occurred in the course of the disease. Since his report a large number of afflicted kinships have been reported from several countries (Thomas, 1975). At present four clinical phenotypes are recognized on the basis of neuropathic patterns and different systemic organ involvement (Mahloudji *et al.*, 1969; Thomas, 1975).

In Japan, Araki *et al.* (1968) first reported patients with FAP from Arao city in Kumamoto Prefecture, one Japanese focus of the disease, and described their clinical picture as being identical to that of Portuguese FAP (Type I). We have recently studied kinships with the disease in another focus in this country and we have found that Japanese FAP consists of a broad clinical spectrum with a variety of systemic organ involvement. In this paper we present the results of our clinicopathological study of Japanese FAP with special reference to the extent of visceral involvement, and also report five kinships with unusual clinical pictures.

METHODS AND CASE DESCRIPTIONS

During the past twelve years we have identified 45 patients with FAP in 31 families in Ogawa village and its environs in Nagano Prefecture, Japan; this is a small village in a mountain valley in the central highlands of this country and constitutes another focus of FAP patients (Kito *et al.*, 1973, 1980) in addition to Arao city in the southern island of Kyushu. All patients had a positive family history for the disease with autosomal dominant inheritance. The diagnosis of amyloidosis was confirmed by histological examination of biopsy specimens from the stomach, rectum, myocardium, skin or sural nerve by polarized light microscopy after Congo red staining. We also observed 20 patients with hereditary generalized amyloidosis with polyneuropathy from five families in Nagano prefecture who had unique clinical manifestations.

TABLE 1. DISTRIBUTION OF AGE AT ONSET IN 45 PATIENTS WITH FAP

Age	*~20*	*20~30*	*30~40*	*40~50*	*50~60*	*60~(yrs)*
No. of patients						
Male	1	12	4	3	3	0
Female	2	7	7	2	0	4

TABLE 2. INITIAL SYMPTOMS IN 45 PATIENTS WITH FAP

Symptoms	*No. of patients*
Dysaesthesiae in the lower limbs	22
Weakness of the lower limbs	3
Anorexia	2
Severe constipation	8
Uncontrollable diarrhoea	2
Impotence	4
Orthostatic fainting	3
Bullous formations	1

Clinical Features of Patients with FAP in Ogawa Village: Common Form

Age of onset. The age of onset varied between the different kinships and among individual patients in the same family, ranging from 16 to 62 yrs, but in half the patients it was between 25 and 35 yrs (Table 1). The mean age of onset was 33.4 yrs for men and 34.2 for women. The sex ratio was nearly equal.

Initial symptoms. The most common initial symptom was dysaesthesiae which developed insidiously in the lower limbs, sometimes associated with intolerable burning or shooting pains in the legs. In the earliest stages, patients experienced the dysaesthesiae only at night or when tired, but later they became constant. Next in frequency came digestive symptoms including severe constipation, uncontrollable diarrhoea, or anorexia. Severe constipation frequently preceded other symptoms by several years. Impotence was another important first complaint in males (Table 2).

Peripheral neuropathy. The clinical manifestations observed in the fully developed stage are listed in Table 3. Two cardinal features were polyneuropathy in limbs and autonomic dysfunction. In typical patients, sensory impairment with dysaesthesiae started in the distal part of the legs and

TABLE 3. CLINICAL MANIFESTATIONS IN 45 PATIENTS WITH FAP

Signs and symptoms	*No.*
Neuropathic signs	
Distal sensory dullness with dissociation	43
Distal amyotrophy and weakness	35
Sensory dullness of the anterior thoracoabdominal wall	26
Facial weakness	4
Facial sensory dullness	3
Bulbar signs	2
Decrease or loss of taste	3
Autonomic symptoms	
Anorexia, nausea and vomiting	26
Alternating constipation and diarrhoea	36
Hypotension	10
Orthostatic hypotension	25
Impotence	18
Dysuria	26
Urinary and faecal incontinence	18
Trophic changes of the skin and anhidrosis	26
Others	
Arrhythmia	13
Congestive heart failure	2
Goitre	4
Macroglossia	8
Oedema	2
Bullous formations	8
Charcot's joint	3
Stokes-Adams attack (all had a pacemaker implanted)	6
Pupillary abnormalities	12
Glaucoma	1
Vitreous opacity	1
Hyperreflexia in limbs	9

progressed in an ascending fashion. Although at an early stage disturbance of thermal and pain sense predominated, later all sensory modalities were lost. In a large number of patients sensory blunting was first noticed in the territory of the peroneal nerve in the feet, and similarly in the upper limbs it preferentially developed in an ulnar nerve distribution. Some patients complained of severe lumbar pain in the early stages, and Lasègue's sign and tenderness over the sciatic nerves were elicited on examination. In addition, about half the patients showed sensory blunting over the trunk, restricted to the anterior thoracoabdominal wall, related to involvement of the distal distribution of the intercostal nerves. Muscular atrophy and weakness with occasional fasciculation appeared a few years after the onset of sensory symptoms. Patients in the advanced stages showed diminished or absent tendon reflexes in all limbs; in the present series 9 patients in the early stages showed exaggerated tendon reflexes in all limbs but with flexor plantar responses. Their tendon reflexes diminished or disappeared within a few years. In the late stages, the cranial nerves were also affected, presenting as facial weakness with lagophthalmos, facial sensory loss, diminution or loss of taste, and bulbar palsy.

TABLE 4. CARDIOTHORACIC RATIO (CTR) AND BLOOD UREA IN FAP (MEAN ±SD)

	Clinical stages			
Measurements	*I*	*II*	*III*	*Normal value*
CTR(%)	41.25±4.92 (n = 10)	43.67±4.00 (n = 14)	53.35±8.90 (n = 7)	< 50
Blood urea (mmol/l)	4.74±1.32 (n = 12)	4.60±1.24 (n = 12)	9.13±6.94 (n = 8)	3.21-7.50

The clinical stages of FAP are three according to Coutinho *et al.* (1980). Stage I: the patient can walk unaided; stage II: patient can move with help; stage III: patient is bedridden.

Autonomic dysfunction. Several autonomic manifestations invariably appeared in the course of the disease. Digestive symptoms, such as severe anorexia, periodic nausea and vomiting, and alternating constipation and diarrhoea with incontinence, were the most common. Orthostatic hypotension with or without generalized hypotension and disturbance of bladder function were other important features. Trophic changes of the skin with anhidrosis were prominent in the limbs, but some patients showed excessive sweating in unaffected truncal skin.

Other symptoms. Besides polyneuropathy and autonomic dysfunction, patients frequently complained of easy fatigability, vague abdominal pain and oral dryness with decreased salivation. Macroglossia, goitre and neuropathic knee or ankle joint degeneration also occurred. Pupillary abnormalities, including scalloped outlines, anisocoria and sluggish reaction to light, were sometimes observed. Glaucoma and vitreous opacity caused by amyloid accumulation were rarely present. Finally, most patients in the advanced stages lost their mobility, became profoundly emaciated, and permanently confined to bed.

Visceral lesions. In this study we paid particular attention to cardiac and renal dysfunction, both of which have been known to be prominent features in nonhereditary generalized amyloidosis.

Cardiopathy. Six patients out of 45 (13%) with the illness for more than seven years experienced the Stokes-Adams syndrome due to sinus arrest or complete atrioventricular block, and required an implanted pacemaker. Congestive heart failure was seen in 2 patients at the terminal stage. We investigated the cardiothoracic ratio (CTR) from chest x-rays in 31 patients at different clinical stages (Table 4). Most patients at the early or middle stages showed neither cardiac enlargement nor clinically overt heart failure, but 2 of 7 in the advanced stage had an enlarged cardiac shadow (CTR $> 60\%$) and congestive heart failure. We performed transvenous right ventricular endomyocardial biopsy on 7 patients, and examined biopsy specimens by light and electron microscopy. Moderate or severe amyloid deposition was observed in all, including 5 patients without cardiac symptoms (Table 5). In the subendocardium, patchy deposits of amyloid were seen, and in other regions most myocardial cells, which were surrounded by rings of amyloid, showed degeneration (fig. 1A, B, C). In severely affected regions only amyloid rings were observed.

Nephropathy. To investigate renal function in FAP we examined blood urea in 32 patients in different clinical stages (Table 4). Patients at the early or middle stage had almost normal values, while 3 of 8 in the advanced stage showed increased blood urea and one bedridden patient was in a state of renal failure (blood urea 26.0 mmol/l). Slight proteinuria was observed in 6 of the 32. Additionally, the mean values of CTR and blood urea in patients in stages I and II were significantly lower than those in patients in stage III ($P < 0.01$), but there were no significant differences between patients at stage I and those in stage II.

TABLE 5. AMYLOID DEPOSITION IN CARDIAC BIOPSY OF FAP

Patient	*Age (yrs)*	*Sex*	*Duration of symptoms (yrs)*	*Clinical stage*	*Cardiac symptoms*	*CTR(%)*	*Amyloid deposition*
1	40	M	2	I	no	50	Moderate
2	38	F	3	I	no	44	Severe
3	46	F	6	I	no	38	Severe
4	59	M	4	II	no	47	Moderate
5	59	M	6	II	no	41	Severe
6	49	F	9	II	S-A	49	Severe
7	49	F	28	III	S-A	50	Severe

The clinical stages of FAP are the same as in Table 4.
M = male, F = female, S-A = Stokes-Adams syndrome.

Hereditary Generalized Amyloidosis with Polyneuropathy Showing Unusual Clinical Features

The following four clinical syndromes, which were reported in part previously (Kobayashi *et al.*, 1978; Ikeda *et al.*, 1981; Yoshioka *et al.*, 1984), were markedly different from those of the common form of FAP. The ancestors of families M and S originated in Ogawa village, but in the other three families (families K, T and H), no genealogical relationship with the families in Ogawa village could be found in the previous four generations (fig. 2). We carried out further studies to clarify the distribution of organs affected by amyloid deposition and the immunohistochemical properties of amyloid fibril proteins in these kinships.

Family K: FAP with cerebellar ataxia and pyramidal tract signs. Patients in this family, with autosomal dominant inheritance, had unique neurological manifestations consisting of cerebellar ataxia and pyramidal tract signs in combination with polyneuropathy and autonomic dysfunction. Ten patients were examined in this family and their clinical features are summarized in Table 6; 5 of them, who were studied in greater detail, showed amyloid deposition in biopsy specimens. Three patients will be described in detail.

The propositus (III-1), a male, first noticed a vague discomfort in his legs when aged 38 yrs. At 45 he experienced recurrent attacks of syncope, which led to the implantation of a pacemaker. About a year later, unsteadiness of gait and impotence appeared, and at the age of 50 yrs, glaucoma caused by amyloid deposition led to visual impairment on the left. Physical examination at 51 yrs revealed postural hypotension and slight cardiomegaly. Neurological examination showed slight weakness in

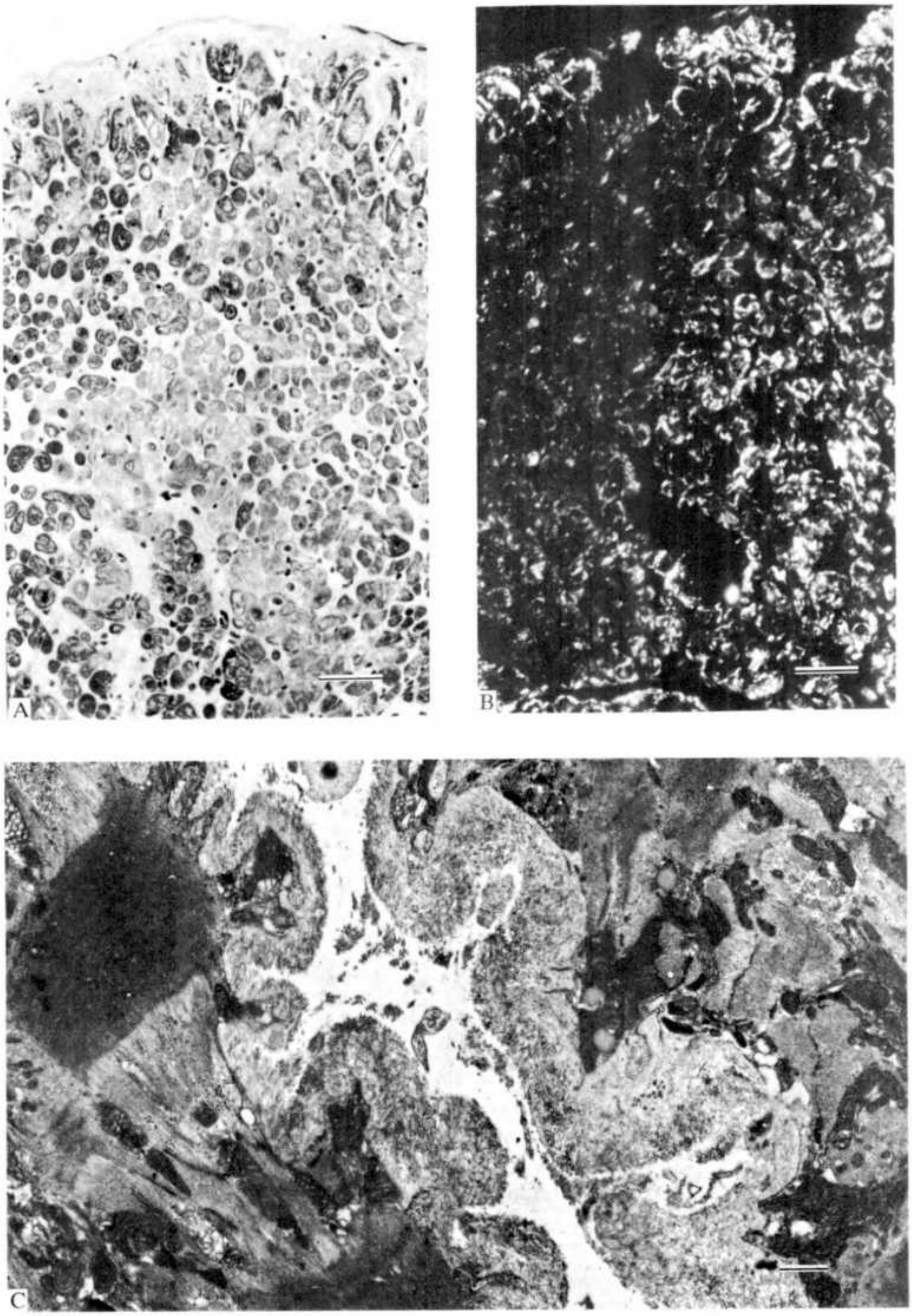
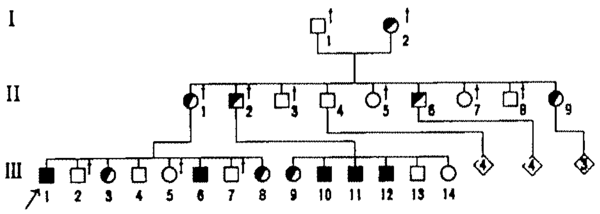
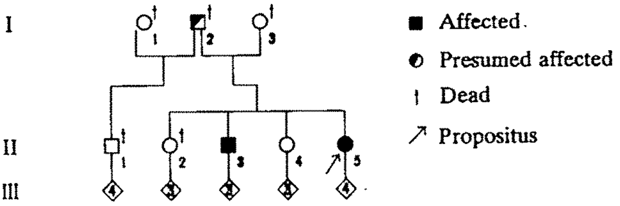


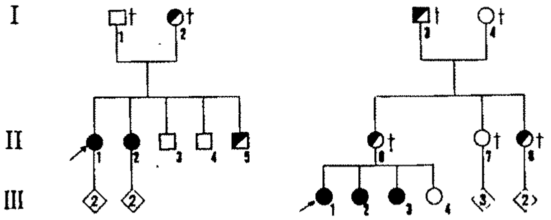
FIG. 1. Cardiac biopsy finding from *Case 5*. A, section stained with haematoxylin and eosin. B, polarized photomicrograph of section stained with Congo red. There is degeneration of myocardial cells with prominent deposition of amyloid in the myocardium (bars = 50 μm). C, electron photomicrograph. Degenerated myocardial cell is surrounded by a dense layer of amyloid fibrils (bar = 1 μm).



Family K

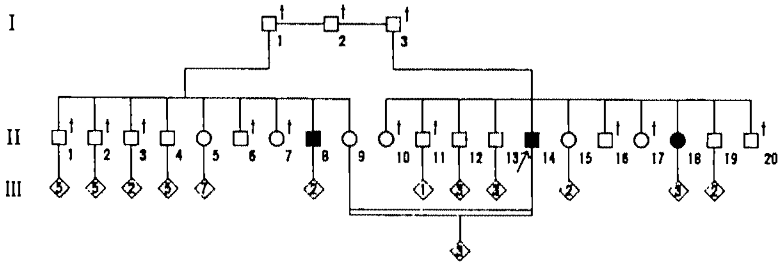


Family T



Family M

Family S



Family H

FIG. 2. Pedigrees of families K, T, M, S and H.

the thigh muscles, decreased pain and temperature sensation in the lower limbs reaching to the inner aspects of the thighs, and an isolated area of sensory impairment, again for pain and temperature, over the left abdominal wall. Light touch was also impaired to a lesser extent, but vibration and position sense was intact. The tendon reflexes were absent at the ankles, but the knee and upper limb jerks were exaggerated. Both plantar responses were extensor. The patient's gait was ataxic and he lost his balance when he attempted to change direction. Electromyography showed denervation potentials in the lower limbs. Sural nerve biopsy revealed loss of myelinated nerve fibres with endoneurial amyloid deposition; rectal biopsy also showed amyloid deposition. One year later he developed an acute left hemiparesis, which was ascribed to cerebral embolism secondary to cardiac arrhythmia. Following this his course was rapidly progressive, with renal failure and intractable congestive heart failure. He died at home at the age of 55 yrs. Autopsy was not performed.

TABLE 6. CLINICAL SUMMARY OF PATIENTS FROM FAMILY K

Patient Age, sex	III-1 55,M	III-3 47,F	III-6 40,M	III-8 36,F	III-9 45,F	III-10 48,M	III-11 44,M	III-12 42,M	II-6 58,M	II-9 49,F
Neuropathic signs										
Upper extremities	++	−	−	−	−	−	−	+	+	−
Lower extremities	+++	+	+	+	+	+	++	−	+	+
Autonomic disorders	++	−	+	−	+	+	−	+	+	−
Central nervous dysfunction										
Incoordination	+	+	−	+	−	++	++	−	+	+
Ataxic gait	+	+	−	−	−	+	+	−	+	−
Hyperreflexia	+	++	++	++	+	++	++	+	++	+
Cardiopathy	+++	/	−	/	/	+	+	+	+	/
Amyloid deposition on biopsy specimen	+	/	+	/	/	+	+	+	/	/

Severity of symptoms except hyperreflexia: − = none, + = slight, ++ = moderate, +++ = severe. Severity of hyperreflexia: + = slightly exaggerated, ++ = prominently exaggerated, / = unexamined.

Case III-10, a brother of the propositus, experienced his first attack of syncope at the age of 40 yrs. On examination, he showed incoordination of the lower limbs and markedly exaggerated tendon reflexes, especially in the legs, but there were no signs suggesting peripheral neuropathy. The ECG indicated second degree atrioventricular block and complete right bundle branch block. Sural nerve biopsy revealed deposits of amyloid in the endoneurium and vascular walls with a slight loss of myelinated nerve fibres (fig. 3). In the following year a pacemaker was implanted because of Stokes-Adams attacks. When reexamined at 48 yrs, he had bilateral vitreous opacities with scalloped pupils and a large goitre. There was slight dysarthria, increased incoordination of the lower limbs, hyperreflexia of all limbs without extensor plantar responses, sensory loss for pain and temperature distally in the legs, but no muscular atrophy or weakness. Laboratory investigation revealed renal dysfunction with proteinuria, and a slightly elevated protein content (0.74 g/l) without pleocytosis in the CSF. A CT scan showed slight symmetric atrophy of the brainstem and cerebellum (fig. 4), but there were no significant changes in the cerebrum.

Case III-11, another brother of the propositus, had a similar clinical course to Case III-10. He was first examined by us at the age of 40 yrs. His speech was slurred and indistinct and he showed hyperreflexia of all extremities and an ataxic gait. Subsequently, dysaesthesiae in the legs and constipation developed, and at the age of 44 he had a pacemaker implanted because of complete atrioventricular block. Neurological reevaluation then revealed scalloped pupils, further deterioration of speech and gait, disturbed rapid pronation-supination movements of the arms and evidence of peripheral neuropathy in the legs. Brain CT showed a similar appearance to Case III-10. Gastric biopsy demonstrated the presence of amyloid (fig. 5).

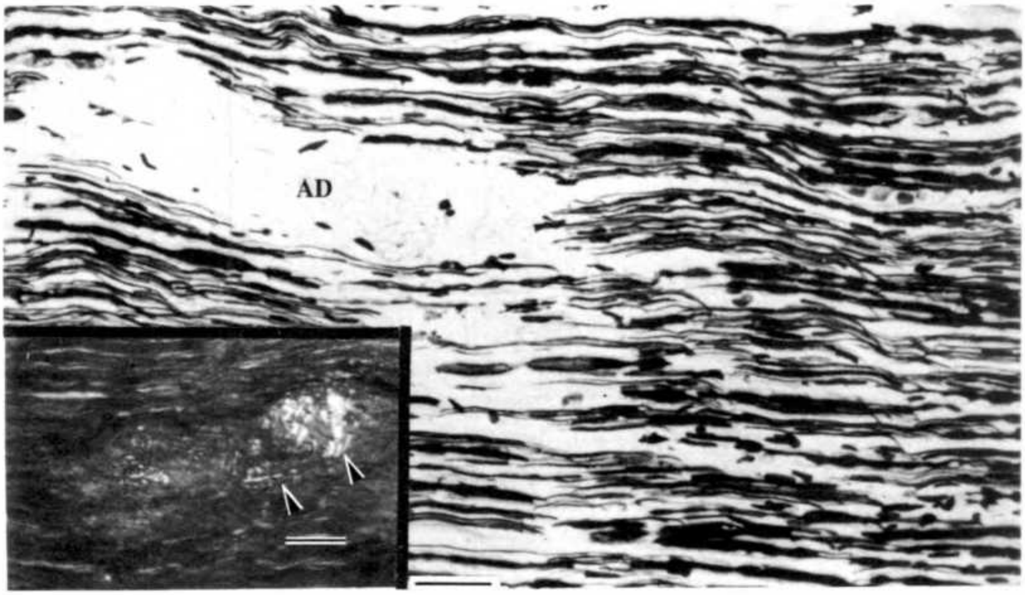


FIG. 3. Sural nerve from *Case III-10*, family K. In a paraffin-embedded section stained with Bodian and Luxol fast blue, myelinated nerve fibres are well preserved and an amyloid deposit (AD) is present. The insert shows an amyloid deposit with birefringence (arrow-heads) with examination of a serial section, stained with Congo red, photographed by polarized microscopy (bars = 50 μm).

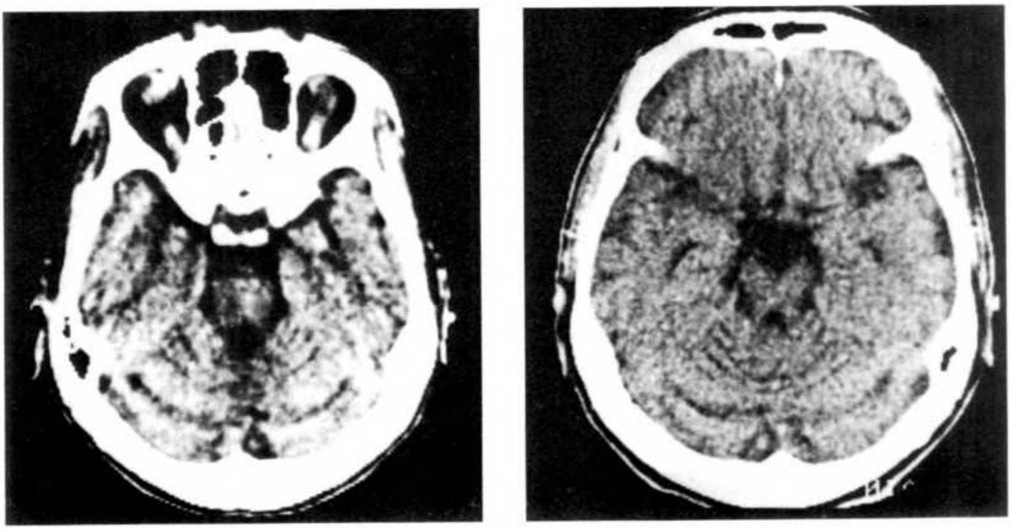


FIG. 4. CT scan from *Case III-10*, family K. Note slight symmetric atrophy of brainstem and cerebellum.

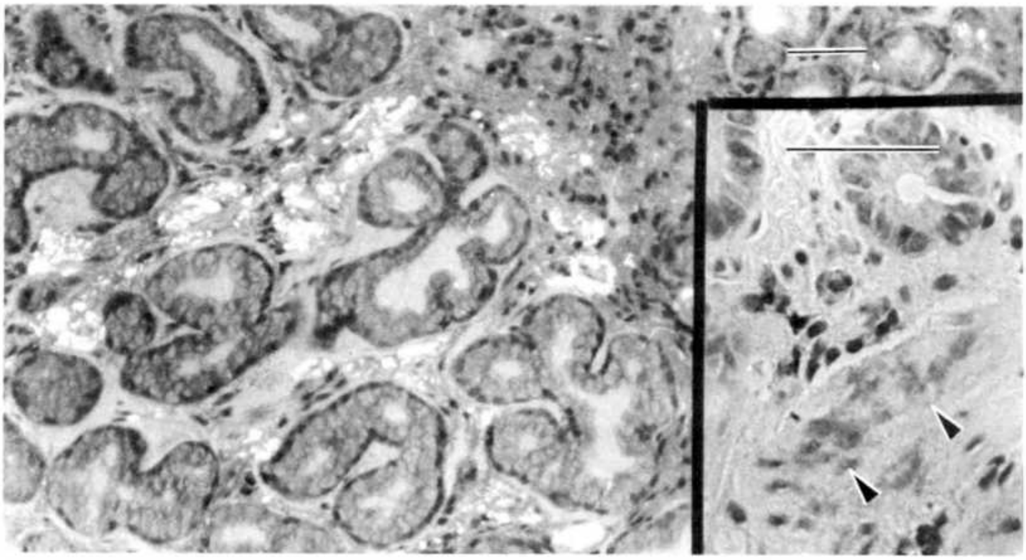


FIG. 5. Gastric biopsy from *Case III-11*, family K. A polarized photomicrograph shows slight amyloid deposition in the muscularis mucosae. The insert shows that deposits of amyloid are positively stained with anti-PA serum (arrow-heads) (bars = 50 μm).

Three other members (I-1, II-1, II-2) were presumed to have the same disorder on the basis of their histories.

Family T: FAP with severe amyloid heart disease. Patients in this family were severely affected by amyloid cardiomyopathy from the onset. They recalled that their father (I-2), who died suddenly at the age of 62 yrs, had suffered from a chronic illness characterized by amyotrophy and dysaesthesiae in the lower limbs, and severe constipation.

The propositus (II-5), a woman aged 53 yrs, was admitted complaining of epigastric discomfort, oedema of the legs and syncopal attacks. Cardiomegaly had been detected five years earlier. Physical examination showed bradycardia, cardiac enlargement and slight hepatomegaly, but no neurological abnormality. The ECG indicated the sick sinus syndrome and echocardiography revealed a thickened cardiac wall with restricted ventricular dilatation. Implantation of a pacemaker relieved her symptoms. When aged 54 she suddenly developed a right hemiparesis and a CT scan indicated cerebral infarction in the distribution of the left middle cerebral artery. A year later numbness in the legs and severe constipation developed and at 57 she was admitted to the Matsumoto National Hospital because of rapidly deteriorating cardiac function. Her heart was markedly enlarged (CTR: 88%) and echocardiography showed a 'granular sparkling appearance' suggesting amyloid deposition in the myocardium (Siqueira-Filho *et al.*, 1981), diminished ventricular movement and massive pericardial effusion. On neurological examination, in addition to the right hemiparesis, pain and temperature sensation was absent in the arms and lower limbs, below elbow and midthigh level, respectively. There was also slight weakness distally in the limbs. Five months later she died from congestive heart failure. At necropsy, cardiac weight was increased (630 g). There was concentric hypertrophy of the myocardium, which was found on histological examination to contain diffuse and heavy deposits of amyloid (fig. 6A, B). Amyloid was also present in the alimentary tract, sympathetic ganglia, peripheral nerves and other systemic organs, but there was no deposition of amyloid in the cerebral parenchyma and vessels.

Case II-3, aged 60 yrs, a brother of the propositus, had suffered from decreased appetite, uncontrollable diarrhoea and oedema in the legs from the age of 56 and, more recently, from frequent syncopal attacks. He had hypotension and an enlarged heart, which produced the typical echocardiographic appearances of amyloidosis. Gastric and rectal biopsies showed amyloid deposition. A year later, peripheral neuropathy developed in the legs and the patient died suddenly at home in the same year.

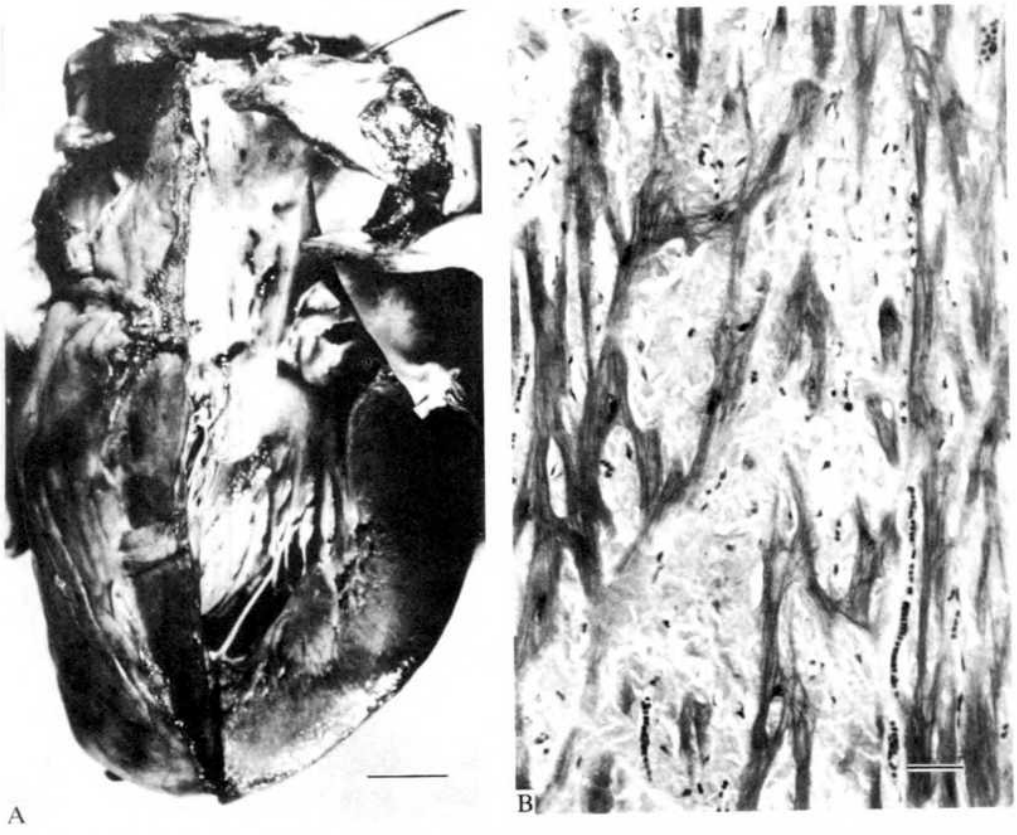


FIG. 6. A, gross appearance of the heart in *Case II-5*, family T. Marked hypertrophy of the left ventricular wall is seen (bar = 2.5 cm). B, histological findings in the myocardium of the same patient (haematoxylin and eosin stain) showing abundant deposition of eosinophilic substance (amyloid) in the myocardium and degeneration of myocardial cells (bar = 50 μm).

Families M and S: FAP with severe nephropathy from an early stage. The clinical features of these 4 patients and 1 patient without nephropathy in the same family are summarized in Table 7. Case II-1 is representative. She was a 52-year-old thin female who had had bilateral glaucoma related to amyloid deposition since the age of 44 yrs. At 48 proteinuria was detected and by the age of 51 yrs, coldness of the legs, constipation and orthostatic fainting had appeared. Physical examination revealed hypotension, slight muscle weakness and pain and temperature sensory loss distally in the legs. Motor and sensory nerve conduction velocity was normal in both upper and lower limbs. Laboratory studies showed albuminuria, increased blood urea and creatinine levels, moderately delayed excretion of phenolsulphonphthalein (15 min excretion in urine: 10%) and reduced creatinine clearance (29 ml/min). The findings in a right kidney biopsy are described in the next section. The neuropathy slowly progressed and symptoms of autonomic dysfunction appeared. Although she was still able to walk unaided, she died of uraemia at the age of 55 yrs. Case II-2 was the younger sister of II-1. She had a similar clinical course with a duration of seven years, and died of uraemia at the age of 52 yrs. At necropsy the kidneys showed massive deposition of amyloid in almost all the glomeruli; vascular and interstitial peritubular amyloid was also present in considerable quantities.

The clinical features of Cases III-1 III-2 from the S family resembled those of the 2 just described from the M family. Proteinuria was detected in both patients in the early stages of the disease and the former suffered from a severe nephrotic syndrome with prominent generalized oedema, but their neurological manifestations closely resembled those of the common form of FAP. Both died from uraemia nine and eleven years after onset. However, Case III-3, with polyneuropathy and autonomic dysfunction, had neither proteinuria nor an increased blood urea concentration at more than ten years after onset.

TABLE 7. CLINICAL SUMMARY OF PATIENTS WITH FAP SHOWING PROMINENT NEPHROPATHY AT AN EARLY STAGE

	Family M		*Family S*		
Patient	II-1	II-2	III-1	III-2	III-3
Age, sex	52,F	51,F	44,F	43,F	37,F
Nephropathy					
Age at detection	48	45	40	35	
Oedema	−	+	+ + +	+	(−)
Proteinuria	1–3 g/day	100–300 mg/dl	5–6 g/day	2–3 g/day	
Blood urea (mmol/l)	12.5	8.9	21.4	7.1	
Neurological manifestations					
Age at onset	51	45	36	38	26
Neuropathic signs					
Upper limbs	−	+	+ +	−	+
Lower limbs	+	+ + +	+ + +	+	+ +
Autonomic disorders	+	+ +	+ + +	+	+ +

Severity of symptoms: + = slight, + + = moderate, + + + = severe.

Family H: FAP with late onset and slow course. All 3 patients in this family developed their symptoms in the sixth decade. The propositus (II-14), noticed the gradual development of dysaesthesiae in the legs and disturbance of gait from the age of 58 yrs. On examination when aged 61, neuropathic signs, including muscular atrophy and weakness, decreased pain and temperature sensation and diminished or absent tendon reflexes were prominent in the lower limbs and moderate in the hands and forearms. Subsequently impotence and gastrointestinal symptoms emerged. At the age of 63 yrs, he had a pacemaker implanted because of complete atrioventricular block, and at 65 he was admitted to hospital because of congestive heart failure due to amyloid heart disease. The polyneuropathy had progressed and he was bedridden. Administration of frusemide relieved his cardiac symptoms, but in the same year he died suddenly from subarachnoid haemorrhage from an arteriovenous malformation in the thoracic spinal cord. Amyloid had accumulated extensively in the heart and peripheral somatic and autonomic nerves. Other systemic organs including the alimentary tract and thyroid gland were also variably affected by amyloid deposition. Amyloid deposition in the CNS was insignificant.

Neurological disabilities in the other 2 patients (II-8, II-18) progressed more slowly. Case II-8, who had no history of hypertension or valvular disease, was found to have atrial fibrillation at the age of 54 yrs and this was considered to be the first sign of the disease. At 61 yrs he lost the sight of his right eye because of amyloid accumulation in the vitreous body. At about 63 yrs he noticed numbness in the legs, and neuropathic symptoms then increased. However, at the age of 68 he could still walk unaided and his autonomic symptoms were not prominent. Case II-18 had experienced shooting pains in the right hand and foot from the age of 51 yrs. At 56 her neurological disabilities were not severe and she was leading a normal daily life. Amyloid deposition in both patients was confirmed by gastric biopsy.

Immunohistochemical study of amyloid fibril protein. To investigate the histochemical properties of amyloid fibril proteins in tissues from these patients with unusual clinical features, we carried out the following study. The unlabelled antibody peroxidase-antiperoxidase (PAP) method (Fujihara *et al.*, 1980) using antisera against prealbumin (PA) and amyloid p component (AP) (obtained from Dako, Denmark), amyloid A (AA) (made in the First Department of Pathology, Yamaguchi University School of Medicine), and immunoglobulin amyloid (ALκ, ALλ) (provided by Professor G. G. Glenner, San Diego) was used on formalin-fixed and paraffin-embedded sections from the stomach of Case III-11, family K, the kidney of Case II-1, family M, the rectum of Case II-5, family T, and the sciatic nerve of Case II-14, family H. The first two specimens were obtained by biopsy and the others at autopsy. Amyloid was deposited in the muscularis mucosae of the stomach in Case III-11, family K, and in the kidney of Case II-1, family M, prominent deposition of amyloid was observed mainly in the glomeruli and vascular walls. Furthermore, submucosal deposits of amyloid were present in the rectum of Case II-5, family T, and many deposits were seen in the endoneurium of the sciatic nerve of Case II-14, family H. All deposits in these specimens were positively stained with anti-PA and anti-AP antisera, but did not react with anti-ALκ, -ALλ and -AA antisera (fig. 5, insert, fig. 7A, B, C; fig. 8A, B).

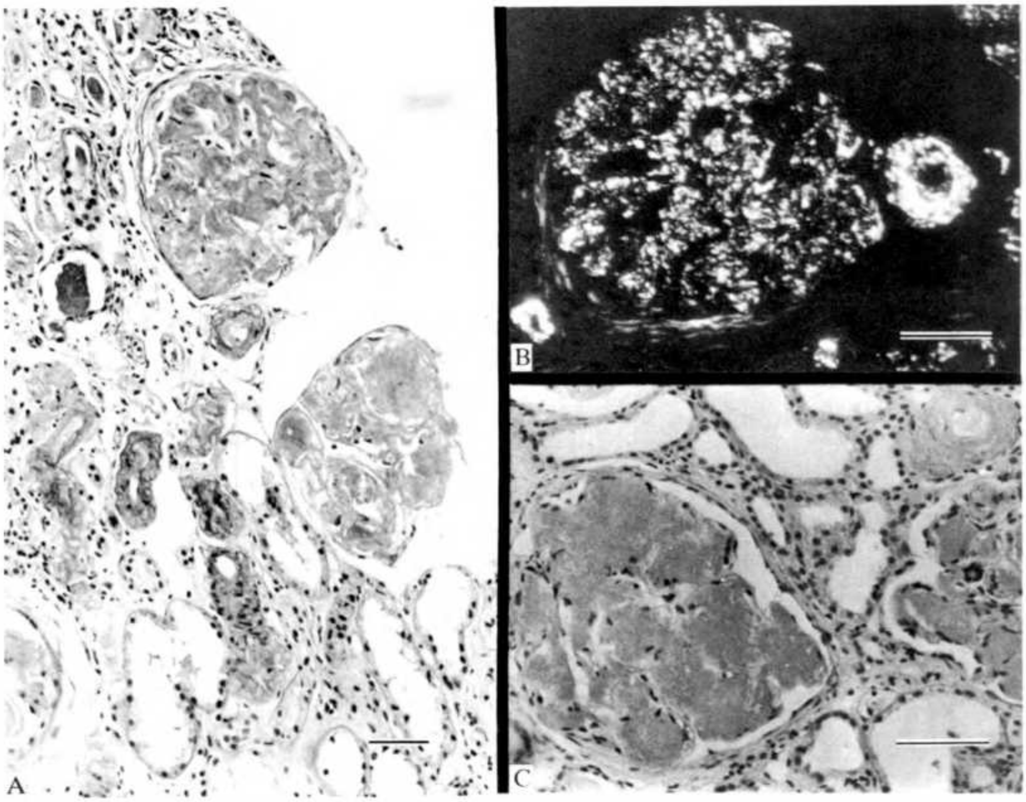


FIG. 7. Renal biopsy findings from *Case II-1*, family M. A, Congo red stain showing severe amyloid deposition in the glomeruli and vascular walls. B, polarized view of the same specimen revealing typical birefringence in the glomeruli and vascular walls. C, Immunohistochemical staining of tissue amyloid. Deposits of amyloid in the glomeruli and vascular walls are positively stained with anti-PA serum (bars = 50 μm).

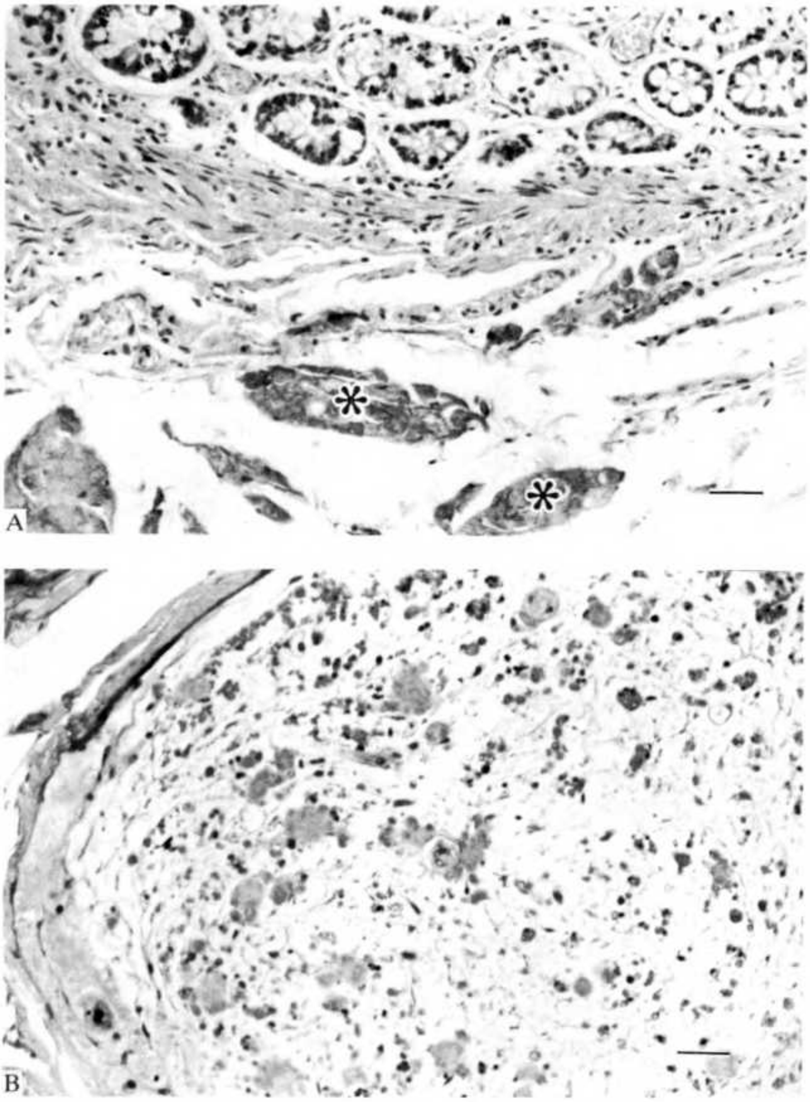


FIG. 8. Immunohistochemical staining of tissue amyloid. A, rectal mucosa of *Case II-5*, family T. Deposits of amyloid (*) in the submucosa show a positive reaction with anti-PA serum. B, sciatic nerve of *Case II-14*, family H. Many deposits of amyloid show a positive reaction with anti-PA serum (bars = 50 μm).

DISCUSSION

The present studies of 65 patients, 50 from Ogawa village and its environs and 15 from other areas in Nagano Prefecture, revealed several new aspects about the clinical features of hereditary generalized amyloidosis with polyneuropathy. In the following we will summarize the clinical features in the common form of FAP and in our families with unusual clinical manifestations, and discuss the spectrum of organ involvement in this disorder.

Age of Onset

The age of onset in our FAP patients from Ogawa village showed a wider range, from 16 to 62 yrs, than that of patients in Arao city, where the range was 30 to 47 yrs (Araki *et al.*, 1968). A recent report on Portuguese FAP (Coutinho *et al.*, 1980) described the age of onset as varying from 13 to 68 yrs, with a mean of 31 for men and 33 for women, which coincides well with our findings. Patients with FAP have been considered to show symptoms at younger ages than those with nonhereditary generalized amyloidosis (Munsat and Poussaint 1962; Kyle and Bayrd 1975), but the age of onset in FAP clearly varies considerably.

Peripheral Somatic and Autonomic Nerve Disorders

The main neurological manifestations in patients from Ogawa village were progressive polyneuropathy starting in the legs, and various autonomic disturbances, satisfying, in principle, the criteria for type I FAP. In the peripheral nerve manifestations of type I FAP, distal sensory loss with an earlier and greater involvement of pain and temperature sensation, has been considered to be a salient feature (Thomas and King, 1974). In addition, the clinical findings of severe lumbar pain, Lasègue's sign and segmental sensory loss, which were observed mainly in patients in the early stages in this study, may suggest the presence of proximal nerve lesions. Pathological studies of sural nerve biopsies have revealed a preferential depletion of unmyelinated and small myelinated nerve fibres in the initial stage of the disease (Dyck and Lambert, 1969; Thomas, 1974) and that nerve fibre degeneration occurs without amyloid deposition in some patients in the early stages (Coimbra and Andrade, 1971*a*, *b*; Carvalho *et al.*, 1976). However, neither of these findings can be ascribed to the local deposits of amyloid in the sural nerve, and it has therefore been thought that amyloid deposits in the dorsal root ganglia or more proximal portions of nerve trunks are important in the pathogenesis of peripheral neuropathy in type I FAP (Thomas and King, 1974). Recently, we found heavy amyloid deposition with prominent nerve fibre changes in the sacral plexus and proximal portion of the sciatic nerve in another 2 autopsied patients with type I FAP, but in their sural nerves amyloid deposition was slight in spite of a total loss of myelinated nerve fibres (Hanyu *et al.*, in preparation). This finding may support the hypothesis mentioned above. Cranial neuropathy has not been reported hitherto in type I FAP, but it occurred in a few of our patients in the advanced stages. Lower cranial nerves were mainly involved, with facial nerve palsy and lagophthalmos being prominent. This cranial neuropathy was readily distinguishable from that of type IV FAP which shows facial paresis and lattice corneal dystrophy from an early stage (Meretoja, 1969).

Autonomic dysfunction was another principal problem for our patients and the bowel symptoms, including periodic anorexia with nausea and vomiting and alternating constipation and diarrhoea, were the commonest and most intractable. In previous studies (Ikeda *et al.*, 1982*b*, 1983), we could not find any correlation between amyloid deposition in the gastrointestinal wall and the severity of digestive symptoms, but we did find severe degeneration of the intramucosal nerves and intramural ganglion cells in the wall of the stomach and rectum in patients with type I FAP. These findings suggest that bowel symptoms in this disorder are mainly attributable to gastrointestinal autonomic nerve lesions.

Disorders of the Central Nervous System

In our series of 45 patients with FAP in Ogawa village, we found 9 with exaggerated tendon reflexes in the limbs, especially the lower limbs, in the early stages, but the significance of this remains uncertain because they did not have any other signs caused by involvement of the CNS. On the other hand, most affected members in the K family, unrelated to anyone in Ogawa village, exhibited disorders of the CNS: cerebellar signs with dysarthria, incoordination in limbs, ataxic gait, and pyramidal signs, all of which were the early clinical manifestations in 3 of them. The CT findings in Cases III-10 and III-11, which indicated symmetric atrophy of the brainstem and cerebellum, were compatible with these neurological manifestations. In addition, most patients showed signs of polyneuropathy with autonomic dysfunction closely resembling those of type I FAP. They also had cardiopathy with disturbances of rhythm and conduction, and deposits of amyloid were confirmed in the biopsies of sural nerve, stomach and rectum. This family thus had the characteristics of generalized amyloidosis.

Amyloid deposition in the CNS in type I FAP was usually unremarkable compared with that in peripheral somatic and autonomic nerves, and no patient with type I FAP has been reported to have CNS symptoms. Independently, an unusual form of hereditary generalized amyloidosis involving mainly the CNS has been reported (Hamburg, 1971; Okayama *et al.*, 1978; Goren *et al.*, 1980). This disorder, which was caused by heavy deposition of amyloid in the leptomeninges and subarachnoid vessels in the whole CNS, developed slowly at about middle age and showed abnormal behaviour, seizures, and recurrent cerebrovascular lesions with coma. With regard to extracranial symptoms, other than a characteristic ocular manifestation with vitreous opacity, the propositus reported by Okayama *et al.* (1978) suffered from severe autonomic dysfunction, and 2 affected brothers described by Hamburg (1971) had neurogenic muscular atrophy of the limbs. The other patients showed no distinct clinical manifestations ascribable to amyloidotic polyneuropathy, autonomic disorder or visceral lesions. Familial cerebral amyloid angiopathy with multiple intracerebral haemorrhage (Gudmundsson *et al.*, 1972) and familial presenile dementia with cerebral amyloid plaques and angiopathy (Worster-Drought *et al.*, 1940, 1944; Corsellis and Brierley, 1954) have also been noted as causing CNS symptoms, but both types are localized forms of amyloidosis restricted to the CNS.

The clinical pictures of patients in the K family in our study differed from those of the familial oculoleptomeningeal amyloidosis or familial cerebral amyloid angiopathy mentioned above in that there were many extracranial symptoms and no recurrent cerebrovascular accidents suggestive of cerebral amyloid angiopathy.

Since some members in the K family suffered from frequent Stokes-Adams attacks, repeated episodes of hypoxia might be considered as one possible cause of the CNS dysfunction. However, in Case III-11, CNS symptoms preceded cardiac dysfunction and the other patients showed further progression of the CNS symptoms after implantation of a pacemaker. Moreover, CT findings in Cases III-10 and III-11 revealed no significant changes in the cerebrum, which is commonly involved by nonspecific ischaemic consequences of cardiovascular disorders (Morrison, 1946; Shy and Drager, 1960). The pathology of the CNS dysfunction in this family has not as yet been investigated. However, it is a fact that symptoms of cerebellar ataxia appeared at about the same time as peripheral somatic and autonomic dysfunction and these combined nervous disorders occurred in all patients in the family. Therefore, although the possibility that hereditary spinocerebellar degeneration and type I FAP can coexist may be undeniable, it seems reasonable to think that the pathogenic mechanism of CNS dysfunction may be related to the systemic deposition of amyloid, and the clinical pattern of the K family suggests a new phenotype of hereditary generalized amyloidosis with polyneuropathy.

Cardiopathy

Clinical patterns of amyloid heart disease are principally divided into two types (Coelho and Pimental, 1961): disturbances of rhythm and conduction, and congestive heart failure. It is generally accepted that in type I FAP the former is common and the latter is rare (Glenner *et al.*, 1978), and in the former disturbances of atrioventricular and intraventricular conduction are prominent (Freitas and Barbedo, 1978; Olofsson *et al.*, 1980; Eriksson *et al.*, 1984*a*). It is clear from our cardiac biopsy findings that in type I FAP amyloid deposition in the heart is present from an early stage. Nevertheless, cardiac insufficiency due to myocardial failure rarely occurs in typical patients with type I FAP. Echocardiographic examination demonstrated that the incidence of cardiac hypertrophy with a granular sparkling appearance is low in type I FAP (Backman and Olofsson, 1983; Eriksson *et al.*, 1984*b*; Hongo and Ikeda, 1986), and low voltage or myocardial infarction patterns on the electrocardiogram are infrequent (Ikeda *et al.*, 1982*a*). Further, on necropsy, deposits of amyloid in the myocardial wall have been observed mainly in the subendocardial region (Hofer and Andersson, 1975). All these findings indicate that amyloid deposition in the whole myocardium in most patients with type I FAP is not sufficiently intense to produce congestive heart failure.

On the other hand, the familial occurrence of amyloid heart disease has been reported. Frederiksen *et al.* (1962) described a Danish family with autopsy-proven generalized amyloidosis, where 5 out of 12 siblings developed severe amyloid cardiopathy with heart failure, and another family with amyloid heart disease was reported by Allensworth *et al.* (1969), showing persistent atrial standstill and congestive heart failure. However, the patients from both families had no extracardiac symptoms.

The predominant clinical manifestation of patients from the T family in our study was cardiac amyloidosis presenting as congestive heart failure, and only in the advanced stages did they show involvement of peripheral somatic and autonomic nerves. The clinical features were distinguishable from those of familial amyloid heart disease by the presence of various extracardiac disorders, and were also different from those of type I FAP. Additionally, on histological examination myocardial damage caused by amyloid deposition was found to be diffuse and severe in comparison with that in type I FAP. We therefore consider this family worth noting as a type of hereditary generalized amyloidosis with severe amyloid heart disease and polyneuropathy.

Nephropathy

Andrade mentioned in his original report (1952) that, at necropsy of patients with type I FAP, the kidney was found to be severely affected by amyloid deposition, but later reports (Silva Horta *et al.*, 1964; Thomas, 1975) stated that there was no nephrotic syndrome or uraemia in Portuguese FAP, and in Swedish FAP amyloid deposition in the kidney was found to be insignificant at necropsy (Hofer and Andersson, 1975). Separately, Van Allen *et al.* (1969) described a family with generalized amyloidosis and polyneuropathy in Iowa (type III), in which 8 members with proven amyloid deposition had also a high incidence of peptic ulcer and nephropathy, and renal failure was the most common cause of death. Therefore the presence of severe nephropathy has been used to differentiate type III FAP from type I.

In the present series of patients from Ogawa village, most patients with type I FAP had relatively well preserved renal function, even in the more advanced stages, but there were another 4 patients from two families in the same area who showed prominent nephropathy from an early stage. In them, renal dysfunction initially manifested itself as marked proteinuria. The blood urea increased a few years later, and all died of uraemia. Pathological study revealed that amyloid had accumulated mainly in the glomeruli and vascular walls. These clinical and histological patterns are the most common manifestations of renal amyloid, which is frequently observed in nonhereditary generalized amyloidosis (Wright and Calkins, 1981), and in this point their clinical pictures were different from those of typical type I FAP. However, their neurological manifestations were identical with those of patients with type I FAP who had no significant nephropathy, and there was 1 affected member with long survival who showed only neurological disabilities and lacked nephropathy. Thus we consider these two families to be a variant of type I FAP, and presume that the degree of amyloid accumulation in the kidney in patients with type I FAP varies considerably among different kinships and even among individual members of the same kinship.

Neurological Manifestations in Patients with Type I FAP with Late Onset

It is of importance whether or not there are clinical differences between patients with early onset and those with late onset. The patients with FAP from the Swedish kinship, who had a late age of onset, were said to have slower clinical courses with longer survival (Andersson, 1970, 1976). But 4 siblings reported by Libbey *et al.* (1984), who came from a kinship of English and German ancestry and developed their symptoms after the seventh decade, showed no special clinical features other than late onset. Similarly, Lima and da Silva in Portugal (1980), in an analysis of 53 patients with type I FAP with an age of onset of over 40 yrs, noticed that the incidence of bowel symptoms was lower, but that the other symptoms and their clinical courses were the same as those of patients who started at younger ages. In family H in the present study, all 3 patients developed their initial symptoms in the sixth decade and the propositus showed a prominent peripheral somatic and autonomic neuropathy with a rapidly progressive course; the other 2 had a rather protracted course and less prominent autonomic dysfunction. Consequently, there seemed to be no significant differences in clinical manifestations and organ involvement between patients with late onset and those with early onset, and we consider that their varied clinical courses may be mainly attributed to interfamilial or intrafamilial differences.

Immunohistochemical Study of Amyloid Fibril Proteins

In 1978, Costa *et al.* reported that the major constituent of amyloid fibril protein in Portuguese FAP was closely related to plasma prealbumin. In Japan a similar result was obtained in FAP patients from Arao city (Tawara *et al.*, 1981) and from Ogawa village (Shoji and Okano, 1981). Recently, Tawara *et al.* (1983) demonstrated that amyloid fibril protein isolated from a Japanese patient with FAP in Arao city was a prealbumin variant with a single substitution of a methionine residue for valine at position 30, and Nakazato *et al.* (1984) found that this prealbumin variant was strikingly increased in the sera of Japanese patients with FAP in Arao city. Therefore, the production of an abnormal prealbumin variant, ascribable to genetic mutation in its phenotypic expression (Sasaki *et al.*, 1984), may be supposed to be the most important factor in the amyloidogenesis of type I FAP.

In the present study we found that amyloid deposits in the tissues in patients from four families showing different clinical features from those of the typical type I FAP patients reacted specifically with antiserum for prealbumin. This suggests that in spite of their unusual clinical manifestations, all amyloid fibril proteins in these patients are immunologically related to plasma prealbumin, and from the recent classification of amyloidosis on the basis of the chemical nature of major constituent proteins of amyloid (Glenner, 1980) these four kinships belong to the same group as type I FAP. Although similar immune reactivities do not necessarily mean that proteins have the same composition of amino acids and we have not yet demonstrated the precise amino acid composition of the amyloid fibril proteins in these families, it is nevertheless noteworthy that the amyloid fibril proteins are apparently similar despite phenotypic variations in hereditary generalized amyloidosis with polyneuropathy. The causes of the clinical heterogeneity in this disorder, however, remain undetermined, and constitute a problem for future investigation.

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GUSTATORY HALLUCINATIONS IN EPILEPTIC SEIZURES

ELECTROPHYSIOLOGICAL, CLINICAL AND ANATOMICAL CORRELATES

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SUMMARY

Of the 718 patients investigated for intractable epilepsy by stereoelectroencephalographic (SEEG) exploration, 30 (4%) manifested gustatory hallucinations as part of their seizures. In 20 patients, it was possible to make some electrophysiological, clinical and anatomical correlates. (1) Gustatory hallucinations occurred as one manifestation of parietal, temporal or temporoparietal seizures. (2) A brief isolated gustatory hallucination was induced mainly by electrical stimulation of the parietal or rolandic opercula in patients with gustatory seizures, in 1 epileptic patient with parietotemporal epilepsy who had never experienced gustatory hallucinations and in another with temporal lobe epilepsy with no history of gustatory manifestations. (3) The electrically-induced seizures, which included a gustatory hallucination as one of the ictal events, were obtained mainly by stimulation of the hippocampus and amygdala. (4) The associated ictal events of a seizure with gustatory manifestations differed depending upon the origin of the seizure. During parietal seizures, they consisted of staring reactions, clonic contractions of the face, deviation of the eyes and salivation. During temporal lobe seizures, the associated events included mainly oral movements, autonomic disturbances, purposeless movements and epigastric or other abdominal symptoms. Seizures affecting both the infra- and suprasylvian regions were characterized by symptoms of both categories listed above. Emotional disturbances were observed mainly when there was an involvement of the cingulate gyrus. (5) When care was taken to avoid methodological errors in the interpretation of the clinical signs occurring after electrical stimulation, it became clear that gustatory hallucinations in man were related to the disorganization of the parietal and/or rolandic operculum. (6) The spontaneous or electrically-induced temporal lobe seizures which included gustatory hallucinations as an ictal event probably spread to the opercular region by a functional reorganization of the connections within these epileptogenic areas.

INTRODUCTION

Taste and smell are neglected senses. Their anatomical pathways remain, at least in part, conjectural. In the field of epilepsy, 'taste and smell' are frequently combined, making the study of each system impossible.

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The sense of taste and gustatory hallucinations have already been studied by several authors, but the location of the cortical centres for taste remains controversial. The anatomist von Bechterew (1900) viewed the insula as a centre for taste. In the previous year, Jackson and Stewart (1899) reported epileptic seizures beginning with a sensation of taste or smell and occurring at the same time as masticatory movements and spitting. They termed such seizures 'uncinate fits' after Ferrier who had expressed the opinion that taste and smell were located in the uncinate gyrus. Anderson (1886), Clarke (1900) and Kennedy (1911) reported gustatory hallucinations associated with temporosphenoidal tumours, and Börnstein (1940) has shown that all anatomical and physiological data point to a cerebral representation of taste separates from that of smell and associated with tactile sensibility of the tongue. This would place it in the inferior point of the postcentral gyrus, the so-called parietal operculum. Then, in 1944, Shenkin and Lewey reported the importance of the parietal operculum in the occurrence of a gustatory aura. Penfield and Boldrey (1937) mapped out the cortical representation of paroxysmal motor and sensory phenomena in man on the basis of electrical stimulation performed during surgery for focal epilepsy in 165 patients. Taste was located in the postcentral gyrus, just above the sylvian fissure, between the representation of 'jaw-teeth' and tongue. Lund (1952) found neoplastic involvement of the temporal lobe in 14 among 21 patients suffering from gustatory auras. In 5 of these 14 patients, the tumour also involved the parietal operculum. Penfield and Faulk (1955) reviewed the results obtained during electrical stimulation of the insula performed during electrocorticography for surgery of focal epilepsy during the period 1945–53. They found 2 patients in whom the electrical stimulation of the insula evoked a disagreeable taste in the mouth and a strange sensation in the abdomen. The authors concluded that the cortical correlate of taste is probably the 'superior sylvian border' and that the abdominal sensations are secondary to movement of the gastrointestinal tract evoked by electrical stimulation of the insula. Motta (1959), who studied 79 patients suffering from miscellaneous neurosurgical disorders, found that corticectomy in the rolandic and parietal regions could result in an ipsilateral gustatory deficit, whereas surgery of the temporal lobe, regardless as to whether or not the amygdala and hippocampus were operated upon, did not lead to any gustatory deficit. However, following this enthusiasm for the parietal operculum as a centre for taste, several papers appeared that again stressed the temporal lobe in the genesis of gustatory hallucinations (Daly, 1958, 1975; Falconer and Cavanagh, 1959; Rasmussen, 1974; Critchley and Rossall, 1978). In conclusion, it appears that there is still a mystery concerning the seat of gustatory manifestations. Do they originate in the operculum, the temporal lobe or the superior circuminsular region? Further, their rarity renders them difficult to study.

The incidence of gustatory manifestations as part of an epileptic seizure is difficult to estimate, especially when authors have grouped gustatory and olfactory manifestations together. Gowers (1909) reported only 1 case with gustatory hallucinations in a series of 1102 epileptic patients. Lennox and Cobb (1933) found 2 such cases in 750 epileptic patients. Gibbs *et al.* (1948) found that a gustatory aura occurred in 1.3% of 300 patients manifesting a 'psychomotor type of discharge' on EEG. Gastaut *et al.* (1955) arrived at a total of 59 cases of gustatory and/or olfactory manifestations in 1000 epileptic patients. Daly (1958) described 16 cases of gustatory hallucinations in 55 patients suffering from 'uncinate fits', and 3% of the 666 patients of Currie *et al.* (1971), suffering from temporal lobe epilepsy, experienced a gustatory sensation during their seizure. Gloor *et al.* (1982) found no cases with gustatory hallucinations in the 35 patients studied to investigate the role of the limbic system in the genesis of experiential phenomenon during temporal lobe seizures. The series of Howe and Gibson (1982), dealing with uncinate seizures which comprised 273 cases of patients with complex partial seizures, included only 9 cases with gustatory hallucinations.

We studied gustatory hallucinations in 30 patients with severe focal epilepsy refractory to medication who were being investigated for possible surgical treatment. The investigations included standard EEGs, drug-induced seizures (with pentylenetetrazol, PTZ; or bemegride, BM) and stereoencephalographic (SEEG) exploration. This latter technique results in a good correlation between clinical manifestations and electrical discharges within specific cortical areas. Thus with the use of SEEG exploration, we attempted to localize cortical areas implicated in the genesis of gustatory hallucinations.

PATIENTS

From 1959 to 1985, 718 patients at the Unité de Recherche sur l'Epilepsie, INSERM 97, underwent SEEG exploration with a view to surgical treatment for severe drug-resistant focal epilepsy. Approximately 305 were suffering from temporal lobe seizures, 309 from suprasylvian seizures and 102 from suprasylvian and infrasylvian seizures. In a retrospective study, we found 30 patients with a history of gustatory hallucinations as one manifestation of their seizures. At least one seizure including gustatory hallucination was recorded during EEG and/or SEEG exploration in 20 patients (group I). For the remaining 10 patients (group II), it was impossible to obtain a seizure with gustatory manifestations during the EEG or SEEG explorations performed in our department. Group I included 14 men (12 right-handed and 2 left-handed) and 6 women (5 right-handed and 1 left-handed). The mean age of the patients in this group (at the time of the investigation) was 22.4 yrs (9 to 41 yrs). The seizures started at a mean age of 9.65 yrs (2 to 34 yrs) and the gustatory manifestations appeared at a mean age of 14.5 yrs (2 to 34 yrs). Group II included only men (8 right-handed and 2 left-handed). The mean age of the patients in this group was 26 yrs (10 to 41 yrs). The seizures started at the mean age of 15.7 yrs (9 months to 41 yrs). The gustatory manifestations appeared at 18.8 yrs (9 months to 41 yrs).

The past history of these 30 patients included 3 cases of encephalitis, 3 cases of head trauma, 3 cases of the 'hemiparetic-hemiconvulsive-syndrome' occurring shortly after birth, 2 cases of respiratory failure at birth, 1 case of chronic otitis, 1 case with a febrile seizure at 6 months, 1 case of near drowning, 1 case of subdural empyema treated surgically, 1 case with a previous operation for a 'capillary angioma' of the temporal lobe. Ten patients had no pertinent antecedents. The pathological lesions found in the patients of both groups are listed in Table 1.

TABLE 1. PATHOLOGICAL LESIONS FOUND IN 30 PATIENTS WITH GUSTATORY HALLUCINATIONS

Case	*Age*	*Sex*	*Methods of evaluation*	*Findings*
Group I				
1	23	M	R temporal lobectomy	Normal
2	28	M	R temporal lobectomy	Normal
3	15	M	R temporal lobectomy	Gliosis of the hippocampus
4	28	M	R temporal lobectomy	Gliosis of the white matter
5	18	F	R temporal lobectomy	Cortical gliosis
6	41	F	R tempororolandic corticectomy	Normal
7	9	M	R tempororolandic corticectomy	Gliosis of the hippocampus
8	23	F	R temporoparietal corticectomy	Arteriovenous malformation in the mesiobasal temporal lobe
9	26	M	R temporal and then parietal corticectomies	Normal
10	17	F	R rolandic corticectomy	'Cortical dysplasia'
11	22	M	R frontal corticectomy	Normal
12	21	M	L parieto-occipital biopsy	Astrocytoma
13	19	M	L parieto-occipital corticectomy	Ulegyria
14	23	M	Radiological investigation	L skull and brain atrophy
15	27	M	Radiological investigation	Normal
16	23	M	Radiological investigation	Normal
17	19	M	Radiological investigation	Normal
18	30	F	Radiological investigation	Cortical atrophy
19	23	M	Radiological investigation	L hemisphere atrophy
20	15	F	Radiological investigation (previous focal encephalitis)	R suprasylvian atrophy
Group II				
21	22	M	R temporal lobectomy	Normal macroscopic lesions seen on pre and postcentral regions during surgery
22	21	M	R temporal lobectomy	Cortical gliosis and vascular proliferation
23	20	M	R temporal lobectomy (previous removal of gyri T1 and T2 for a 'capillary angioma')	Normal
24	24	M	L temporal and parietal corticectomy (previous meningitis)	Normal
25	34	M	L temporal lobectomy	Normal
26	44	M	L mesiobasal frontal biopsy	Fibrillary astrocytoma
27	39	M	L frontotemporal biopsies	Fibrillary astrocytoma
28	17	M	Radiological investigation	Normal
29	19	M	Radiological investigation	Normal
30	20	M	Radiological investigation	Normal

METHODS

The methodology of these investigations has been described in detail in several papers (Bancaud *et al.*, 1965; Bancaud and Talairach, 1975; Talairach *et al.*, 1974, 1975). Briefly, the EEG investigations were performed on the basis of previously collected data: *clinical* (history, clinical evolution of the seizures, neurological examination); *electrophysiological* (mainly EEG recording of spontaneous seizures); and *anatomical* (stereotactic neuroradiological investigation, Talairach *et al.*, 1967; Szikla *et al.*, 1977).

The choice of the cortical structures to be explored by the intracerebral depth electrodes was defined on the basis of the presumed localization of the 'epileptogenic' area. For the anatomical correlations, the topography of the electrodes (5 to 15 electrode contacts) was precisely determined with regard to the AC-PC (anterior commissure-posterior commissure) reference stereotactic system and to their distance from the sylvian fissure, the rolandic fissure and the midline (Talairach *et al.*, 1967; Szikla *et al.*, 1977). Three-dimensional angiography can define precisely the position of the different cortical sulci (Szikla *et al.*, 1977). The AC-PC baseline and its perpendiculars, the VAC line (the vertical line to the posterior border of the anterior commissure) and the VCP line (the vertical line to the anterior border of the posterior commissure) applied to the neuroradiological data of each patient, constituted a common denominator allowing for detailed anatomical correlations (Talairach *et al.*, 1967). The intercommissural length (between the superior border of the AC and the inferior border of PC) was specified for every patient.

During the SEEG exploration itself, emphasis was placed on the electroclinical correlates. Every clinical detail was carefully recorded and written on the SEEG recording to permit a further analysis of the seizures. The patients, who were awake during the whole procedure, were observed continuously by two neurologists and were filmed by two video cameras. We paid particularly close attention to the occurrence during the seizure (early or late) of a gustatory hallucination. The associated ictal events of the hallucination were recorded and listed: clonic contractions of the face, arm or body, special sensations in the mouth, throat, stomach or abdomen, salivation, chewing or licking movements, spitting, autonomic disturbances, changes in mood, and altered states of consciousness.

For electrical stimulation through depth electrodes during SEEG exploration, single stimuli or stimulus trains were used. Single stimuli, with an intensity of 2.5 mA and lasting 1 ms, were delivered at a rate of 2.5/s for 50 s. Stimulus trains consisted of 50 stimuli/s lasting 1 ms each. The stimulus strength for each train varied from 4 to 12 V and the duration was from 1 to 5 s.

RESULTS

In the 20 patients from group I, we studied a total of 73 seizures where the patient experienced a clearly appreciated abnormal taste in the mouth as part of his clinical presentation. These seizures were recorded in EEG and/or SEEG explorations (some patients underwent 2 or 3 SEEG explorations) (*see* Fig. 1); 63 seizures originated in the right hemisphere and 10 in the left. For seizures that occurred only during EEG recording, there was only 1 patient, who had a single spontaneous seizure. For seizures occurring only during SEEG exploration, there were 12 patients who had a total of 14 spontaneous seizures, 2 seizures induced with PTZ, 2 induced with BM and 25 evoked by electrical stimulation. For seizures that occurred both during EEG and SEEG exploration, there were 7 patients who had a total of 7 spontaneous seizures in EEG, 1 seizure induced with PTZ in EEG, 4 induced with BM in EEG, 6 spontaneous seizures in EEG, 1 induced with PTZ in SEEG and 10 evoked by electrical stimulation. Gustatory hallucinations occurred in 10 patients during temporal lobe seizures, in 6 during parietal seizures and in 4 during parietotemporal seizures. In 3 patients, the gustatory hallucination occurred during any of temporal, parietal or parietotemporal seizures.

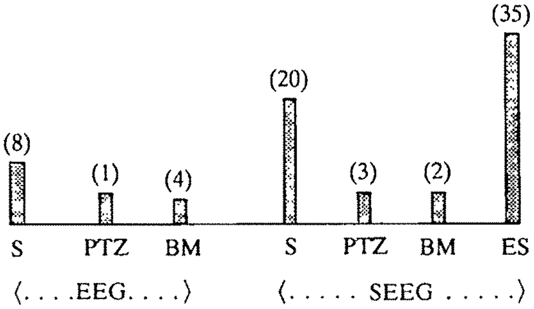

FIG. 1. Type of seizure with gustatory hallucinations recorded in EEG and/or SEEG explorations. S = spontaneous seizures; PTZ = pentylenetetrazol-induced seizures; BM = bemegride-induced seizures; ES = seizures induced by electrical stimulation.

Seizures Induced by Electrical Stimulation

An isolated brief gustatory hallucination was elicited in 7 patients by electrical stimulation (fig. 2). Stimulus trains were used in all cases with the exception of Case 11 where single stimuli were favoured.

Case 1 (before temporal lobectomy). Stimulation of the right amygdala (electrode A) electrode contacts 1-2, 8 V, 50/s, 1 ms. 'I tasted something rising up in my throat, like at the end of my fits.' The afterdischarge spread to the right hippocampus.

Case 1 (after temporal lobectomy). Stimulation of the lower part of the right parietal operculum (electrode K), 1 cm above the sylvian fissure, 4 mm behind the rolandic fissure, 17 mm above AC-PC line, 5 mm behind VAC line. Electrode contacts 1-2 (43 mm from midline), 10 V, 50/s, 1 ms. 'I tasted something in my throat as usual, it tasted like a cigarette.' No afterdischarge. The same stimulation evoked the same response three times in sequence. Electrode contacts 3-4 (48 mm from midline). 'I tasted something very weak.' The afterdischarge spread to the parietal operculum.

Case 8. Stimulation of the right rolandic operculum (electrode R'), 2 mm above the sylvian fissure, 4 mm in front of the rolandic fissure, 17 mm above AC-PC line, 7 mm behind VAC line. 1-2 (39 mm from midline), 12 V, 50/s, 1 ms. The patient grimaced at the disagreeable taste. 'I taste something in my throat.' Local afterdischarge.

Case 11. In this patient, the right insula was drawn forward because of frontal atrophy secondary to previous evacuation of a subdural empyema. Stimulation of the rolandic operculum (electrode R''), 15 mm above the sylvian fissure, 5 mm anterior to the rolandic fissure, 16 mm above the AC-PC line, 8 mm anterior to the VAC line. 1-2 (30 mm from midline), 2.5 mA, 50 s, 1 ms, 2.5/s. 'I taste something in the throat, as if I had smoked a cigarette.—A bitter taste?—Yes.' No visible afterdischarge. 2-3. 'Its starting again, the taste starts in the stomach, it rises and falls.' Afterdischarge, involving superficial and deep rolandic operculum, less than 20 s.

3-4. 'Again, it starts here (sternum), I'm out of breath, I feel like choking, it squeezes my head, it makes my mouth dry, the taste is less bitter, less strong, weaker.' No visible afterdischarge.

4-5 (45 mm from midline). 'Here it is, I can't breathe, as if I were put asleep with a mask; at the same time, the taste rises up, the temples feel tight. The taste is very bitter, very unpleasant.' This time, the taste appeared only at the end of the stimulation. No visible afterdischarge.

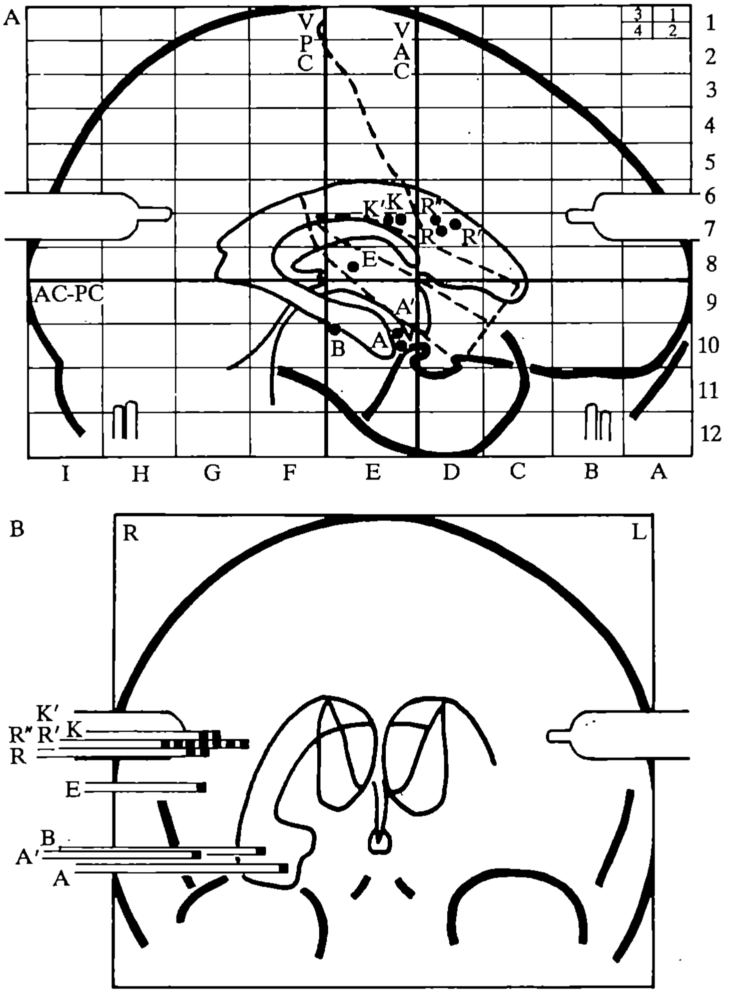

FIG. 2. Exact locations where implanted electrodes induced an isolated brief gustatory hallucination when stimulated electrically. A, lateral view; B, anteroposterior view. K, Case 1; K', Case 20; R, Case 14; R', Case 8; R", Case 11; A, Cases 1, 5; E, Case 10. For explanation of other abbreviations, *see* Methods.

Stimulation of the most superficial part of the R" electrode 1-2 (51 mm from midline), 2.5 mA, 50 s, 1 ms, 5 s. Three seconds after the end of the stimulation, the patient said 'I taste something rising up and falling differently this time, very slowly.' The taste was still bitter and dry, like the first cigarette in the morning. It involved the internal part of the lips and of the cheeks and the whole tongue. No visible afterdischarge.

2-3 (55 mm from midline). This time, the gustatory sensation was less well defined and associated with deviation of the eyes to the left.

Case 14. Stimulation of the lower part of the right rolandic operculum (electrode R), 2 mm anterior to the rolandic fissure, 13 mm above the sylvian fissure, 7 mm anterior to VAC line, 15 mm the AC-PC line.

1-2 (47 mm from midline), 6 V, 50/s, 1 ms. 'An unpleasant taste, impossible to describe, like the beginning of a fit.' No visible afterdischarge.

3–4 (51 mm from midline), 8 V, 50/s, 1 ms. 'It shook in my mouth. I tasted something odd, like a rotten apple, different from the taste during my usual fits'. No visible afterdischarge.

Case 20. Stimulation of the right parietal operculum (electrode K′) 3 mm above the sylvian fissure, 4 mm behind the rolandic fissure, 21 mm above AC-PC line, 5 mm behind VAC line.

1–2 (44 mm from midline), 6 V, 50/s, 1 ms, 1 s. 'I tasted something'. There were clonic contractions of the left corner of the mouth. Local afterdischarge.

2–3, 8 V, 50/s, 1 ms, 1.5 min. 'A bitter taste'. Tonic contraction of the left corner of the mouth. Local afterdischarge, less than 20 s.

3–4 (47 mm from midline), 8 V, 50/s, 1 ms, 5 s. 'The taste is less intense.' Tonic contraction of the left corner of the mouth. Local afterdischarge.

Case 10. Stimulation of the medial part of the right T1 gyrus (electrode E), 2 mm from T1 sulcus, 4 mm above CA-CP line, 14 mm behind VAC line.

3–4 (45 mm from midline), 10 V, 50/s. 'I started to have a fit' (fit = taste for this patient). Afterdischarge spread to the posterior part of T1 gyrus.

Case 5. Stimulation of the anterior part of the right T2 gyrus (electrode A). 1–2 (45 mm from midline), 12 V, 50/s. 'I am about to have a fit, a taste.' No visible afterdischarge.

In these 7 cases, the afterdischarge was absent, was limited to the stimulated electrode (local afterdischarge), or spread only to the immediately adjacent electrode. It must be stressed that Case 8 never experienced any gustatory hallucination in the past nor during other EEG or SEEG exploration performed in this Institute.

In 8 patients, electrical stimulation evoked a seizure, which included gustatory hallucinations and other signs and symptoms. The regions stimulated included the right rolandic operculum (Case 9), the right parietal operculum (Case 20), the right hippocampus (Cases 5, 7, 16, 18), the right amygdala (Cases 4, 5, 16), the left hippocampus (Case 13) and the left amygdala (Case 13). The following are illustrative cases.

Case 9 (after temporal lobectomy). Stimulation of the right rolandic operculum (2 mm behind the rolandic fissure, 5 mm above the sylvian fissure, 8 mm above CA-CP line, 6 mm behind VAC line.

1–2, 8 V, 50/s. Stimulation induced a rapid and large EEG discharge at the rolandic operculum and at the right ascending parietal gyrus. At 20 s after the electrical manifestation the patient had some difficulty speaking and there were clonic contractions of the left corner of the mouth. 'Do you taste anything?' 'Yes'. The patient was no longer able to talk although he retained his ability to write. The tongue and the jaw were deviated to the left. The left arm stiffened, the eyes deviated upwards and to the left. This was followed by clonic contractions of the left side of his body, a stiffening of both legs and a deviation of the eyes to the right. After this, flushing of the abdomen was noted and the eyes returned to the neutral position. The electrical discharge spread across the right hemisphere to the posterior part of T2, to the occipital cortex and to the supramarginalis gyrus but remained more prominent at the rolandic operculum.

Case 4. Stimulation of the right amygdala.

2–3, 8 V, 50/s. There was a local afterdischarge which spread to the right posterior hippocampus, right T2 gyrus and to the temporo-occipital junction. At 10 s after the end of the stimulation, the patient indicated that he felt something in his throat and said that he tasted something. The pupils were dilated and the face flushed and later, oral movements were noted. 'It is like my usual fits.'

Brief spontaneous electrical paroxysms were associated with a sensation of taste in the mouth in 2 cases. In Case 10, the paroxysms were recorded during SEEG exploration. They lasted 6–8 s each and were localized at the parietal operculum. The taste was associated with salivation, swallowing, contraction of the masseters and deviation of the left corner of the mouth to the left. In Case 6, the spontaneous paroxysms were also recorded during SEEG exploration, at the right hippocampus; they lasted 20–40 s each. By the time the patient felt the taste, she licked her lips, cleared her throat, felt nauseated and complained that her upper lip felt like cardboard.

We analysed all seizures with gustatory manifestations occurring during SEEG, including spontaneous seizures, drug-induced seizures and seizures evoked by electrical stimulation, from both the electrical and clinical standpoints. Only SEEG explorations with electrodes covering both the suprasylvian regions and the temporal lobe were considered free from any possible methodological error. Only 14 patients were included in this analysis (a total of 20 SEEG explorations).

TABLE 2. OCCURRENCE OF GUSTATORY HALLUCINATIONS AND ASSOCIATED ICTAL EVENTS IN RELATION TO THE TOPOGRAPHY OF THE SEIZURES

Cases	*1*	*9*	*10*	*14*	*20*	*7*	*15*	*16*	*19*	*1*	*5*	*7*	*1*	*2*	*4*	*5*	*10*	*13*	*18*
Gustatory hallucination	e	d	c	f	c	g	h	i	c	a	b	b	a	a	a	a	a	c	b
Timing	e	l	l	e	e	l	e	l	e	l	e	l	e	l	l	e	e	e	e
Clonic contractions	+	+	+	+	+++	+	−	−	+	−	+	−	−	−	−	−	−	−	−
Deviation of the eyes	−	−	+	+	−	−	−	−	+	−	+	+	−	−	−	−	−	−	−
Somatic sensation	−	+	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−
Visceral sensation	+	−	−	−	−	−	+	−	−	+	+	−	+	−	+	−	−	−	−
Salivation	−	+	+	+	−	−	−	−	+++	−	−	−	−	+	−	−	−	−	−
Oral movement	−	−	+	−	−	−	−	+	−	+	−	+	−	+	−	−	−	+	+
Purposeless movement	−	−	−	−	−.	+	−	+	−	+	−	−	−	+	−	−	−	−	+
Autonomic disturbance	−	−	−	+	−	+	−	+	+	+	−	+	−	−	+	−	−	+++	−
Alteration in mood	−	−	−	−	−	−	−	+	−	+	+	−	−	−	−	−	−	+	−
Staring reaction	+	+	−	+	−	−	−	+	−	−	−	+	−	+	−	−	−	−	−
Topography of seizures	P	P	P	P	P	PT	PT	PT	PT	P	PT	T	T	T	T	T	T	T	T
											Cing								

P = parietal; PT = parietotemporal; T = temporal; Cing = involvement of the cingulate gyrus by the epileptic discharge. Gustatory hallucinations: a, 'a taste'; b, 'bad'; c, 'bitter'; d, 'tart'; e, 'cigarette'; f, 'bad apple'; g, 'piquant juice'; h, 'rusty iron'; i, 'artichoke'. For timings of seizures, e = early, l = late.

The seizures tended to spread rather uniformly. When they started in the anterior mesiobasal regions of the temporal lobes (amygdala and hippocampus), they spread successively to the anterior, middle and/or posterior temporal convexity as far as the supramarginal and lingual gyri. The epileptic activity either remained within these areas or extended to the suprasylvian areas via a circuminsular route to the F2 gyrus and the anterior part of the cingulate gyrus. However, most seizures did not spread more anteriorly than the parietal and rolandic opercula. Thus seizures originating in the amygdala or hippocampus adopted a more or less complete perisylvian route, originating on the infrasylvian side. Seizures originating within the suprasylvian region were very rare (at least during the SEEG explorations which were used to investigate simultaneously the suprasylvian and infrasylvian areas). They occurred spontaneously in only 1 patient (Case 14). These seizures started at the opercula (rolandic and parietal) and spread to the ipsilateral and contralateral amygdalae and anterior temporal cortex and to the contralateral

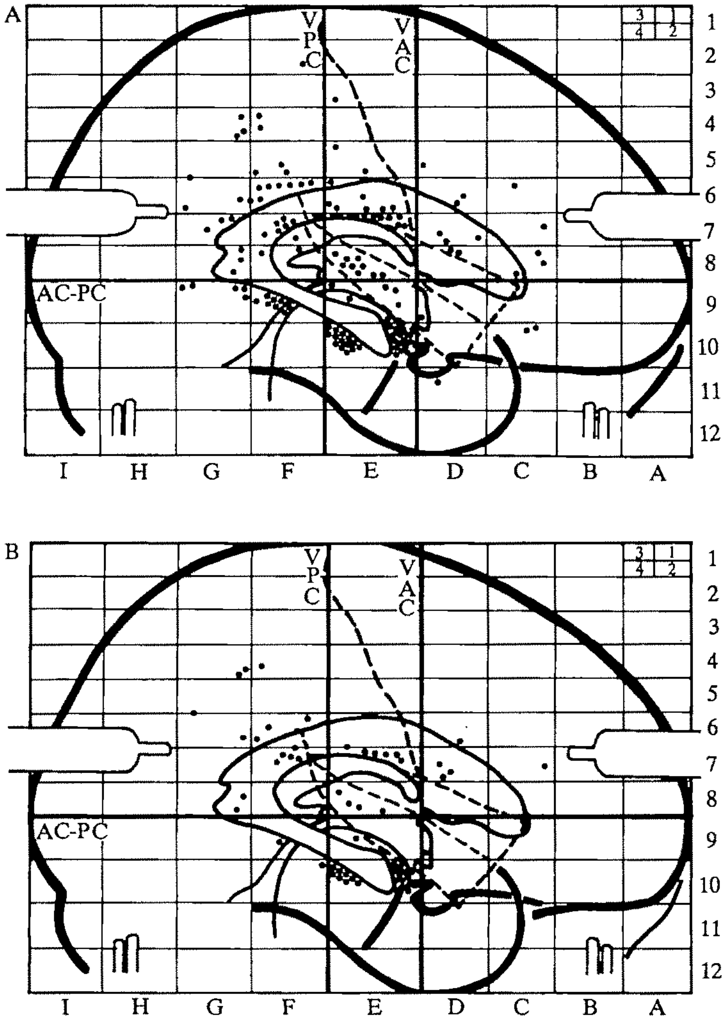

FIG. 3. A, locations of all the implanted electrodes for the 14 patients investigated (20 SEEG explorations). B, electrodes implicated by epileptic activity at the moment when the 14 patients experienced gustatory hallucinations during their seizures.

opercula. In Case 19, a PTZ-induced seizure started at the left parietal operculum and left F3 gyrus and spread to the left temporal pole and to the left hippocampus. It then involved all the suprasylvian and infrasylvian electrodes (left F3 gyrus, parietal operculum, temporo-occipital junction, angular gyrus, T1 gyrus, hippocampus and amygdala).

Fig. 3 shows all the areas immediately involved by a seizure when the patients experienced a gustatory hallucination. There is a clear perisylvian distribution of the epileptic activity and frequent involvement of the amygdala and hippocampus. Table 3 shows the clinical signs and symptoms recorded during these seizures.

TABLE 3. CLINICAL MANIFESTATION AND LOCALIZATION OF THE LESIONS FOR GROUP II PATIENTS DURING THE GUSTATORY SEIZURES

Case	*Description of usual seizures*	*Localization of lesions*
21	Onset of the taste is early. A taste which resembles that of bile. The patient has dysaesthesiae of the L wrist; there is a slow abduction of the L corner of the mouth; then, clonic contractions of the L side of the body.	R temporal lobectomy in the past. Macroscopic lesions (?) in the R suprasylvian region seen during surgery
22	Epigastric sensation which ascends to the throat, a taste in the mouth, swallowing.	R temporal lobe focus on EEG
23	The patient stares at an object, finds it beautiful; salivation and bitter taste in the mouth.	R temporal focus on SEEG
24	Pain in the epigastrium, shivers, a bitter taste, nausea.	L temporal lobe and parieto-occipital foci on SEEG
25	A lump in the throat; oral movements. The patient is no longer able to talk. Phosphenes in the R upper fields. When the patient regains consciousness he complains of a bitter taste.	L temporal lobectomy
26	The patient experiences the sensation of his whole body exploding, then olfactory or gustatory hallucinations: 'Its like ether or acetone'.	L frontal astrocytoma involving the frontobasal areas and the posterior and mesial frontal regions
27	Bitter or sweet taste; then, sensation in the epigastrium and throat.	L frontotemporal astrocytoma
28	Sensation of an intense heat which ascends from the stomach to the mouth accompanied by a disagreeable taste.	L temporoparietal focus on EEG
29	Abdominal pain which ascends to the throat and returns to the abdomen, followed by a bitter taste in the mouth.	
30	Bitter taste, hypersalivation, swallowing, spitting, at times vomiting. Angry outburst accompanied by shouting episodes.	Epileptic activity in R temporal lobe and superior margin of the R sylvian fissure on SEEG. R cingulate gyrus also involved

Some clinical features seemed to be more frequent in relation to the regions involved by the seizure: during parietal seizures, the ictal events associated with the gustatory hallucination were mainly a staring reaction, clonic contractions of the face, deviation of the eyes and salivation. Chewing and other oral movements were rarely observed. In parietal seizures, the gustatory hallucination was either an early subjective symptom or occurred later. It might or might not be specific. During temporal lobe seizures, the more prominent clinical signs were oral movements (chewing, swallowing, lipsmacking, etc.), autonomic disturbances (pupillary dilatation, tachycardia, facial blushing, nausea and vomiting), purposeless movements and epigastric or abdominal symptoms. The gustatory hallucinations usually occurred early in temporal lobe seizures. The taste was usually not described in detail but rather in more general terms such as 'bitter', 'unpleasant' or 'a taste'. Seizures involving temporal lobe and suprasylvian regions at the same time were characterized by signs and symptoms of both categories listed above. The taste in this category was more often specific ('rusty iron', 'artichoke', 'mussel', 'oysters' . . .). Emotional disturbances were found mainly when there was involvement of the cingulate gyrus.

To validate these findings, we reviewed the patients of group II (clear history of gustatory hallucinations but no seizure with gustatory manifestation recorded in our Institute). A summary of the case records of these patients is given in Table 3. Group II patients never experienced a gustatory hallucination during the multiple EEG and SEEG recordings, so that the electroclinical correlates described in Table 4 were rather imprecise. Nevertheless, Case 21 (with suprasylvian lesions and a temporal lobectomy) manifested clonic movements of the face and arm as an associated ictal event of the gustatory hallucination. In this latter case, the hallucination was described with precision: 'bile'. In this group of patients, epigastric sensations were frequent and they were usually mobile, 'ascending' to the throat or mouth and 'returning' to the stomach. These sensations were present when the lesions implicated the temporal lobe, the temporoparietal or the temporofrontal regions.

Gustatory Phenomena

Quality of the taste (*see* Table 2). The gustatory hallucinations were usually unpleasant. The taste was qualified as bitter, acid, tart, sweet or disgusting. Rarely it was described more specifically as 'toasted peanut', 'rusty iron', 'blood', 'bile', 'ether', . . . This was more frequently the case when the epileptic activity involved the parietal or the parietotemporal regions. Usually the gustatory hallucinations were not lateralized. However, Case 9 spoke of an abnormal taste on the *left* side of the tongue (the epileptic focus was in the *right* hemisphere). For 14 of 20 patients, the taste experienced during the seizures induced with BM, PTZ or evoked with electrical stimulation, was similar to that experienced by these patients during their spontaneous seizures. In 3 cases, the taste occurring after electrical stimulation differed from the usual gustatory hallucination. In Case 11, the 'acid taste' was replaced by a cigarette-like taste when the rolandic operculum was stimulated. In Case 14, the 'awful bitter taste' obtained by stimulation of contacts 1–2 of the right rolandic operculum electrode gave way to a taste of 'bad apple' when the stimulation implicated the electrode contacts 3–4. Case 16, who used to experience a taste of 'grilled peanut', spoke of a taste of 'artichoke' during the stimulation of the right hippocampus and of 'mussels' and then of 'oysters' during electrical stimulation of the right amygdala. For some patients, the gustatory hallucinations occurred either as part of a temporal lobe seizure, a temporoparietal seizure or a parietal seizure (*see* Table 2). With these different electrical topographies, the seizures differed in quality with regard to the occurrence of taste (early or late, specific or not) and the associated ictal events of the taste. The following are illustrative cases.

Case 1, parietal seizure (stimulation of the parietal operculum).

1–2. The patient stopped counting: 'I tasted something that climbed up to the back of my throat, in the usual fashion, it tasted like a cigarette.'

3–4. The patient stopped counting. There were clonic contractions of the lips. 'I tasted something very mild.'

Case 1, suprasylvian seizure with involvement of the posterior cingulate gyrus (spontaneous seizure during SEEG exploration, 1.5 min). The patient opened his eyes, licked his lips, seemed anxious and looked around. He manifested purposeless movements of the left arm. 'I felt very light, and tasted something in my mouth.'

Case 1, temporal lobe seizure (stimulation of the right amygdala produced an afterdischarge which involved the right hippocampus). 'I taste something which seems to climb up to the throat, like at the end of my usual fits.' The patient rubbed his chest with his right hand, his eyes were deviated to the right, he looked around. 'Did you have a fit?' 'Yes, I felt very light.'

Case 5, suprasylvian seizure (BM-induced seizure during SEEG exploration). The patient's eyes deviated to the left, there was an abduction of the left arm, clonic contractions of the left side of the face. The contractions subsequently became generalized and the eyes deviated to the right. At the end of the seizure, the patient said she had anticipated it by a taste, a smell and an anxious feeling (note that the cingulate gyrus was involved).

Case 5, temporal lobe seizure (stimulation of the right amygdala induced an afterdischarge which spread to the cingulate gyrus). 'I felt anxious and experienced a sensation in the mouth. It was the beginning of an average fit.'

Intensity of the taste. In electrically-induced seizures, the intensity of the taste was related to the depth of stimulation in 2 cases. In Cases 11 and 20, the taste was less intense when the electrical stimulation involved the more superficial electrode contacts of the rolandic and parietal opercula electrodes.

Frequency of gustatory manifestations in the seizures of the patients. The gustatory hallucinations were part of the usual seizures since the onset of the epilepsy in 15 out of 30 patients, whereas in 11 out of 30 patients, the gustatory hallucinations appeared as late as 16 yrs (from 3 to 16 yrs) after the onset of the epilepsy. Four patients had never experienced gustatory manifestations during their seizures in the past and manifested them for the first time during SEEG exploration. In Case 17 a 'taste of chloroform' appeared after the injection of PTZ (no change on EEG). The gustatory hallucinations of Case 12 occurred after the injection of BM and during stimulation of the left hippocampus (each time, the taste was described as 'bad and odd'). Case 8 experienced only once 'a taste in the throat'. This occurred during electrical train stimulation of the rolandic operculum (local afterdischarge). Case 9 experienced his first gustatory hallucinations after temporal lobectomy, 'a tart taste in the mouth' (*see above* for electrographic manifestations).

In only 1 patient (Case 14) could the seizure be evoked at will. This patient experienced gustatory hallucinations, similar to the spontaneous ones, by taking some liquid or food. In our laboratory, the seizures appeared from 30 to 50 s after the ingestion of water or food.

The frequency of the gustatory seizures was not consistent. It varied from patient to patient and was more or less similar to the frequency of the other types of seizure exhibited by these patients. The artificial occurrence of an isolated sensation of taste by electrical stimulation could be elicited by a single stimulus (Case 11) or by stimulus trains (Cases 1, 5, 8, 10, 14, 21).

Evolution after Surgery

Out of the 30 patients, 17 underwent surgery for epilepsy (9 temporal lobectomies, 2 frontal corticectomies, 2 tempororolandic corticectomies, 1 temporoparietal corticectomy, 1 parieto-occipital corticectomy and 1 temporal and then parietal corticectomy). Following operation, 14 of the 17 patients experienced no further gustatory hallucinations even if some of them still exhibited some kind of seizure. In Case 21, the temporal lobectomy did not modify the characteristics of the seizures, including gustatory manifestations. As previously mentioned, Case 9 experienced his first gustatory hallucination after the temporal lobectomy. For Case 1, the temporal lobectomy had a peculiar effect on the seizures: following the operation, the hallucination occurred at the beginning of the seizure instead of at the end, as was the case before operation.

DISCUSSION

Gustatory hallucinations are rare. Among 718 patients investigated with SEEG from 1959 to 1985, we found only 30 patients, (4%) who manifested gustatory hallucinations as part of their seizures. This percentage of gustatory hallucinations in a series of 'epileptic patients' (including miscellaneous types of epilepsies and of seizures) is similar to that found in the literature. The age, sex and right hemisphere predominance of the epileptic focus for these 30 patients are consistent with the data for the epileptic population as a whole (Talairach *et al.*, 1974). These features depend upon the selection made, that is, these patients were considered for surgical treatment because of the intractable nature of their epilepsy. For 20 patients, it was possible to record a seizure with gustatory manifestations and to derive electrophysiological, clinical and anatomical correlates.

An isolated brief gustatory hallucination could be elicited from six different regions when electrically stimulated: right rolandic operculum in 4 patients, right parietal operculum in 1 patient, right amygdala in 1 patient, right hippocampus in 1 patient, medial aspect of the right T1 gyrus in 1 patient and the anterior part of the right T2 gyrus in 1 patient. A seizure with gustatory manifestations was induced by electrical stimulation of three different regions: right hippocampus in 4 patients, right amygdala in 1 patient, left hippocampus in 1 patient. Thus taste seemed to be elicited mainly in two areas: the rolandic and parietal opercula and the anterior part of the temporal lobe, mainly the anterior mesiobasal part.

The literature dealing with gustatory hallucinations also highlights the dichotomy concerning anatomical origin of taste, temporal versus suprasylvian. Most of the patients described in the literature were not investigated by SEEG exploration or electrocorticography. In these patients, the anatomical-clinical correlates were inferred from the abnormalities found on the EEGs or from the postmortem examination of the brain. The patient of Shenkin and Lewey (1944), who had an arteriovenous malformation located in the sylvian fissure with the greatest dilatation over the lowest portion of the postcentral gyrus, exhibited an aura of a sour taste seemingly originating in his stomach, followed by nausea, unconsciousness and a generalized convulsion. Penfield and Faulk (1955), when stimulating the insula during electrocorticography, obtained visceral sensory or motor, responses, or both, at times producing a gustatory hallucination. Their patient G.B. is of interest. This 25-year-old boy developed focal seizures characterized by a sensation under the left costal margin, an unpleasant taste in the mouth and masticatory movements. During the electrocorticography, an epileptogenic focus was demonstrated in the central region just above the sylvian fissure. Stimulation of the postcentral gyrus at the border of the sylvian fissure, at a depth of 1 cm from the surface, was followed by swallowing and the patient complaining of an unpleasant taste: 'a sickish taste in my throat spreading to my mouth.' He said this was the same taste that he had before his usual attacks. The lower ends of the precentral and postcentral gyri were then removed up to the sensory area of the thumb and this dissection was carried down to the surface of the insula. He was readmitted, a year later, for continuing epileptic seizures. These seizures were characterized by 'an unpleasant sensation' in his stomach. The gustatory aura no longer occurred during his seizures. The patient was reinvestigated and stimulation of the posterior and superior portions of the insula reproduced the disagreeable taste and the sensation in his stomach, similar to that experienced before the first operation. This case illustrates that the sense of taste is probably located in the frontal and parietal opercula as well as in the superior border of the insula. It also shows that epileptic gustatory hallucinations can disappear in spite of an incomplete removal of all the gustatory epileptogenic cortex. The results obtained after corticectomy are thus not indicative of the exact origin of the gustatory hallucinations.

The patient of Anderson (1886), a 23-year-old male, presents an example of temporal lobe seizures with gustatory manifestations. He complained of a 'sensation in his mouth, a rough, bitter sensation' and then a 'peculiar sensation passing down the right arm into the hand, then up the spine from the level of the shoulder to the head, finally spreading over the back of the skull as a cold sensation'. He frequently shivered during the seizure and generally saw the same scene, a scene from his childhood. The attacks lasted a few minutes. This patient was suffering from a large tumour arising from the pituitary gland and undermining the posterior three-fourths of the temporosphenoidal lobe. For Falconer and Cavanagh (1959), there was a striking correlation between the incidence of 'taste and/or smell' and lesions involving the mesial temporal structures, especially the amygdala, the uncus and the anterior part of the hippocampal gyrus. In their series, the sensation of taste occurred only once as a solitary aura with these temporal lesions. In the other cases, it was preceded by one of the following auras: visceral sensations (mainly epigastric or abdominal), perceptual illusions, visual hallucinations, fear or tinnitus.

In our series, seizures arising from the suprasylvian region were of the following type: clonic contractions of the face, deviation of the eyes, salivation. The gustatory hallucinations in this type of seizure appeared early or late and were often described as a specific taste: 'cigarette', 'rotten apples', 'taste of regurgitation' . . . On the other hand, seizures originating in the temporal lobe had the following features: announcement of the seizure, gustatory hallucination, oral movements, autonomic disturbances, epigastric or abdominal symptoms, looking around.

The role of the anterior temporal lobe in the genesis of a gustatory sensation seems difficult to explain from an anatomical standpoint: taste buds on the tongue, palate, pharynx, tonsils, epiglottis and, in some people, the mucosa of the lips and cheeks, contain a group of individual gustatory receptor cells. For the tongue, the facial nerve (anterior two-thirds) and the glossopharyngeal nerve (posterior third) carry visceral afferent impulses from taste solutions in contact with the gustatory receptors to the rostral part of the nucleus solitarius in the medulla oblongata. From there, fibres ascend bilaterally in the region of the medial parvocellular part of the posteromedial ventral nucleus of the thalamus. Data from cortical ablation in the squirrel monkey (Benjamin and Burton, 1968) show that the cortical projection area for taste is in the frontal and parietal opercula and in the limen insulae. Bagshaw and Pribram (1953) demonstrated that ablation of the cortex limited to the anterior supratemporal plane or to the parietal operculum is not sufficient to produce ageusia in Macaca mulatta. Only extensive removal of the whole anterior sylvian cortex (including parietal operculum) produces marked and prolonged ageusia. For these authors, the anteromesial temporal cortex could subserve gustatory discriminative mechanisms while anterior sylvian (insular operculum and anterior supratemporal) cortex could subserve more 'primary' gustatory function.

From animal studies, there is some anatomical and electrophysiological evidence showing that the amygdala receives gustatory signals. The existence of direct interconnections between the cortical gustatory area (agranular insular cortex) and the amygdala has been suggested by horseradish peroxidase tracing (Veening, 1978; Lasiter, 1982; Ottersen, 1982; Saper, 1982), autoradiography (Norgren and Grill, 1976; Krettek and Price, 1977), silver impregnation (Turner, 1981) and electrophysiological studies (Yamamoto *et al.*, 1984) in rats. The physiological significance of such interconnections remains to be determined. Norgren (1976), using electrophysiological and anatomical data, demonstrated that some of the gustatory axons in the dorsal pons of rats convey gustatory information to the hypothalamus and amygdala. The central nucleus of the amygdala, which is the main target of taste afferents in the amygdala, also receives dopaminergic afferents. It has been suggested that these dopaminergic afferent fibres interact with taste afferents and contribute to taste-motivated behaviour in the rat (Mogenson and Wu, 1982). However, in man, morphine, a dopamine agonist, modifies olfactory sense but not taste (Macht and Macht, 1940). In Parkinson's disease, the reduction of dopamine is often associated with absent or diminished smell (Ansari and Johnson, 1975), whereas taste is not modified. On the other hand, changes in taste are a well known side-effect of L-DOPA therapy (Siegfried and Zumstein, 1971). This side-effect is greatly reduced when L-DOPA is administered with a decarboxylase inhibitor which suggests that the cause of changes in taste from L-DOPA therapy is probably more extracerebral than intracerebral. There is thus no convincing evidence that cerebral dopaminergic influences play a role in taste function in man. Also the role of the amygdala in gustatory function in man remains to be proven. In our patients, it was possible to induce a seizure with gustatory manifestations by electrical stimulation of the amygdala in 4 patients and an isolated gustatory hallucination in only 1.

If great care is not taken to avoid methodological errors, it is impossible to appreciate the role of the regions whose dysfunction leads to gustatory hallucinations. The epileptic brain behaves as though there were a modification of the usual anatomical connections (Bancaud, 1981; Buser and Bancaud, 1983). We regard the epileptogenic area as a 'functional neoformation' (Bancaud, 1980). Given this reorganization, it is not surprising that a gustatory hallucination, even if it is isolated, could be induced by the electrical stimulation of different, seemingly unrelated areas. To localize the seat of taste by electrical stimulation, precautionary measures must be taken to avoid this pitfall. (1) It must be established that the electrical stimulation does not induce an afterdischarge elsewhere. For example, consider the following situation. A gustatory hallucination is created by the stimulation of the amygdala or the hippocampus. It would be an error to conclude that these regions represented the seat of taste if the presence of an afterdischarge spreading to the opercula had not been excluded by the appropriate monitoring. (2) The chronological appearance of the ictal events must be analysed. Thus if the gustatory hallucination is a late event during an electrically-evoked seizure, the likelihood that it is related to the disorganization of the stimulated region is diminished, even absent. (3) The only good control would be to obtain a gustatory hallucination in a patient who had never experienced such hallucinations. (4) The best criterion implicating the role of a given region as the seat of taste—as for perceptual hallucinations in general—would be the occurrence of an electrically-evoked gustatory hallucination in a patient whose usual seizures do not suggest the involvement of the stimulated region.

We respected these criteria and it became obvious that gustatory hallucinations, in man, are related to the disorganization of the central and/or parietal opercula. This conclusion was based on the following observations. (1) Gustatory hallucinations occurred as an isolated and prominent manifestation of parietal seizures and with parietal and/or rolandic opercula electrical stimulation, whereas in temporal lobe seizures, they were intermixed with many other subjective symptoms. (2) Electrical stimulation of the parietal and rolandic opercula induced gustatory hallucinations in epileptics already experiencing this phenomenon (Cases 1, 11, 14, 20) and in 1 epileptic patient with parietotemporal seizures who had never before experienced such symptoms (Case 8). In addition, a gustatory hallucination was induced by electrical stimulation of the parietal operculum in a patient suffering from temporal lobe epilepsy who had never complained of gustatory manifestations. (3) Furthermore, temporal lobectomies failed to abolish gustatory hallucinations in 3 cases (Cases 1, 9, 21). A parietal corticectomy relieved Case 9 from his gustatory hallucinations. Cases 1 and 21 did not have a second operation. However, in the 718 patients investigated for intractable epilepsy in our Institute, 13 of 305 patients with temporal lobe seizures exhibited gustatory hallucinations, which is a higher percentage (4%) than that found in patients suffering from suprasylvian seizures (6 of 309 patients, i.e. 2%) or from suprasylvian and infrasylvian seizures (3 of 102 patients, i.e. 3%). We propose that this discrepancy could be related to the functional reorganization of the spreading pathways within the epileptogenic areas and that in some forms of temporal lobe epilepsy, there are patent connections between the mesiobasal temporal lobe and the opercula.

The study of gustatory evoked potentials in man may represent a promising means of investigating the cortical localization of the sense of taste. Cohen *et al.* (1957) studied the evoked cortical responses after stimulation of the chorda tympani (seventh cranial nerve) and the trigeminal branch of the lingual nerve in cats. Cortical cells responding only to taste solutions applied to the tongue (and not to mechanical stimulation of the tongue) were found ipsilaterally at depths between 1.8 and 2.3 mm below the surface of the cortex, 'dorsal to the rhinal fissure and the presylvian sulcus, caudal and ventral to the lateral tip of the coronal sulcus and cranial to a small dimple which is found rostral to the tip of the suprasylvian sulcus'. Funakoshi and Kawamura (1971) studied evoked gustatory potentials in man but did not localize the cortical areas responsible for taste. They recorded the cerebral activity from the temporal region, on the scalp. We plan to record in SEEG gustatory evoked potentials on both the opercula and the mesiobasal temporal lobe to search for (1) the location of the maximum amplitude of these potentials and (2) the presence of a constant latency between potentials from these two regions which could suggest an anatomical pathway.

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DISTURBANCE OF SEQUENTIAL MOVEMENTS IN PATIENTS WITH PARKINSON'S DISEASE

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SUMMARY

The following sequences of two single movements were examined in 10 patients with Parkinson's disease and compared with the performance of 9 normal subjects of similar age. (1) Isometric opposition of thumb and fingers to a force of 30 N ('squeeze'), followed by isotonic elbow flexion ('flex') through 15° with the same arm. (2) 'Squeeze' with the left hand followed by 'flex' with the right elbow. (3) Isotonic opposition of thumb and fingers ('cut') through 90° followed by isotonic 'flex' with the same arm. (4) Isotonic elbow 'flex' followed by isometric 'squeeze' with the same arm. All movements were self-paced. Subjects were given instructions to move as rapidly as possible and to start the second movement immediately after the end of the first.

Patients were slower than normal when each single movement was performed separately. There was a further decrease in speed when two movements were executed sequentially. This was due (1) to an increase in movement duration of each of the component movements, especially the second, and (2) to an increase in the pause between the first and second movements. In both normals and patients, there was no correlation between the times taken to perform the first and second movements of any of the four sequences that were studied. Because of this we suggest that the two components of the sequence remained under the control of two separate motor programs.

When performing the sequential tasks, normal subjects automatically chose an interval between the onsets of the two separate movements of about 230 ms, even in tasks in which the duration of the first movement was less than 200 ms. If normal subjects were instructed to begin the second movement with an interonset interval of less than 200 ms, the speed of the second movement was much slower. Patients with Parkinson's disease automatically chose a much longer interonset interval of 400–500 ms. In addition, they exhibited difficulty in switching from the first to the second movement in the sequence.

We suggest that the problems exhibited by patients with Parkinson's disease when they try to perform two rapid sequential movements can be seen as a deficit in the capacity to switch from one motor program to another within an overall motor plan.

INTRODUCTION

There have been a large number of investigations into the control of single one-joint movements in patients with Parkinson's disease (*see*, e.g., Hallett and

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Khoshbin, 1980). However, there have been relatively few studies of the control of more complex (and perhaps more commonplace) combinations of two or more tasks such as those pioneered by Schwab and colleagues (Schwab *et al.*, 1954, 1959; Talland and Schwab, 1964). In a previous paper (Benecke *et al.*, 1986*a*) we showed that patients with Parkinson's disease had additional difficulties in performing two movements at the same time, over and above the deficits seen when each movement was performed separately. If patients were asked to squeeze an isometric force transducer and flex the elbow, or to perform isotonic thumb and finger opposition and flex the elbow simultaneously, then the movements always were slower than when each component was executed separately. The additional slowness of movement in the 'flex' and 'squeeze' task correlated better with clinical estimates of akinesia than performance of separate single movements.

An additional feature emerged from these experiments. In both patients and normals, there was no correlation between the times taken to execute the two components of the simultaneous movement. Carter and Shapiro (1984) have shown that, for a complex movement that is governed by a single motor program, the movement times of each component of the movement covary when the duration of the whole movement increases. Since there was no correlation between the two component movements we suggested that in these particular tasks, the two movements remained under the control of two separate, but superimposed, motor programs. It was possible that the additional deficit seen in patients with Parkinson's disease represented a difficulty in executing more than one program at the same time.

The present investigation extends these observations to sequential movements. Sequential movements play an important role in normal motor behaviour. For example, we change rapidly from sitting to standing and to walking, or we grasp an object first and then place it in a new position. In an investigation of normal subjects (Benecke *et al.*, 1986*b*) we found that movement times during the sequential performance of an elbow flexion and an isometric or isotonic opposition of thumb and fingers were not correlated. Thus these sequential movements were not guided by one common complex motor program, but by two separate simple motor programs. However, irrespective of whether these movements were carried out with the same arm or with opposite arms, they could only be performed with maximal speed when there was a delay of about 230 ms between their onsets. At shorter interonset latencies, the speed of the second movement was progressively reduced. This finding led to the conclusion that in normal subjects switching from one motor program to another is activated with an optimal minimal delay of about 230 ms.

From a clinical point of view it is well known that patients with Parkinson's disease have difficulty in the execution of sequential movements, but it is not known why. Are motor sequences slow, simply because each simple movement is slow? Is the timing between sequential movements disturbed? Are sequential movements slower than separate simple movements? It will be shown that the performance of motor sequences is disturbed in all three of these ways in patients with Parkinson's disease.

PATIENTS AND METHODS

Ten men with at least one year's history of idiopathic Parkinson's disease were studied. These were the same patients tested for their performance of simultaneous movements in a previous study (*see* Table 1 of Benecke *et al.*, 1986*a*), which gives clinical details, treatment, degree of akinesia, rigidity and tremor evaluated clinically, and performance on a pegboard test and two-point touching test. All but 1 were treated with L-DOPA and showed obvious benefit. Seven of the patients were studied 10–18 h after the last oral dose of L-DOPA (OFF therapy); 2 other patients were tested ON therapy, but they still had considerable motor impairment.

The results obtained in the patient group were compared with a group of 9 normal subjects. The mean age of this normal group (47.0 yrs; range 31–67) was slightly but not statistically significantly ($P > 0.05$) lower than that of the patients (58.1 yrs; range 37–76). All subjects were right-handed and gave informed consent for the procedures used.

Tasks

Four types of sequential movements were analysed. (1) Unilateral (right) isometric opposition of thumb and fingers ('squeeze') followed by an isotonic elbow flexion ('flex') (unilateral 'squeeze then flex' task). (2) An isometric 'squeeze' with the left hand followed by an isotonic elbow 'flex' with the right arm (bilateral 'squeeze then flex' task). (3) A unilateral (right) isotonic opposition of thumb and fingers ('cut') followed by an elbow 'flex' ('cut then flex' task). (4) A unilateral (right) elbow 'flex' followed by an isometric hand 'squeeze' ('flex then squeeze' task).

Each individual movement was also analysed when executed separately. The general instruction for all tasks was: first, execute each movement of the sequences as rapidly as possible; second, initiate the second movement immediately after termination of the first. Task 1 was also tested with slightly changed instructions: the subjects were asked to modify voluntarily the latency between the onset of both movements (interonset latency (IOL)) so that the second movement occurred earlier (i.e. during) or later (i.e. after) than termination of the first movement. In addition, simple visual reaction times were recorded for isotonic flexion of the elbow or isometric squeeze of the fingers and thumb. A warning tone was given at randomized times (2–5 s) before the go-signal. The subjects were informed verbally in advance whether the response should be a 'flex' (15°) or a 'squeeze' (30 N). After 5 practice trials 10 consecutive 'flex' and 'squeeze' responses were collected.

In order to achieve comparable movements between subjects, initial start and final target positions, as well as the movements themselves were displayed as vertical bars on an oscilloscope screen 60 cm in front of them (fig. 1); however, no emphasis was placed on accuracy.

Apparatus

Unilateral 'squeeze then flex' task. Subjects were seated comfortably with their right arm abducted to 90° at the shoulder. The semipronated forearm rested on a lightweight manipulandum which was pivoted so as to be coaxial with the elbow joint. The angular position of the elbow joint was recorded by a potentiometer mounted on the manipulandum. At the end of the manipulandum, adjusted according to the length of the forearm, was a U-shaped bar of aluminium which could be grasped between the thumb and fingers. A strain gauge was mounted on one of the vertical arms of the U so that the force of squeeze could be monitored (fig. 1A). The separate movements of 'squeeze' (up to 30 N) and 'flex' (over an angle of 15° from a starting angle of 135° flexion), as well as a sequential movement ('squeeze then flex'), had to be performed.

Bilateral 'squeeze then flex' task. For this task the force transducer was removed from the manipulandum and placed at the end of the left arm rest, where it could be grasped with the left hand.

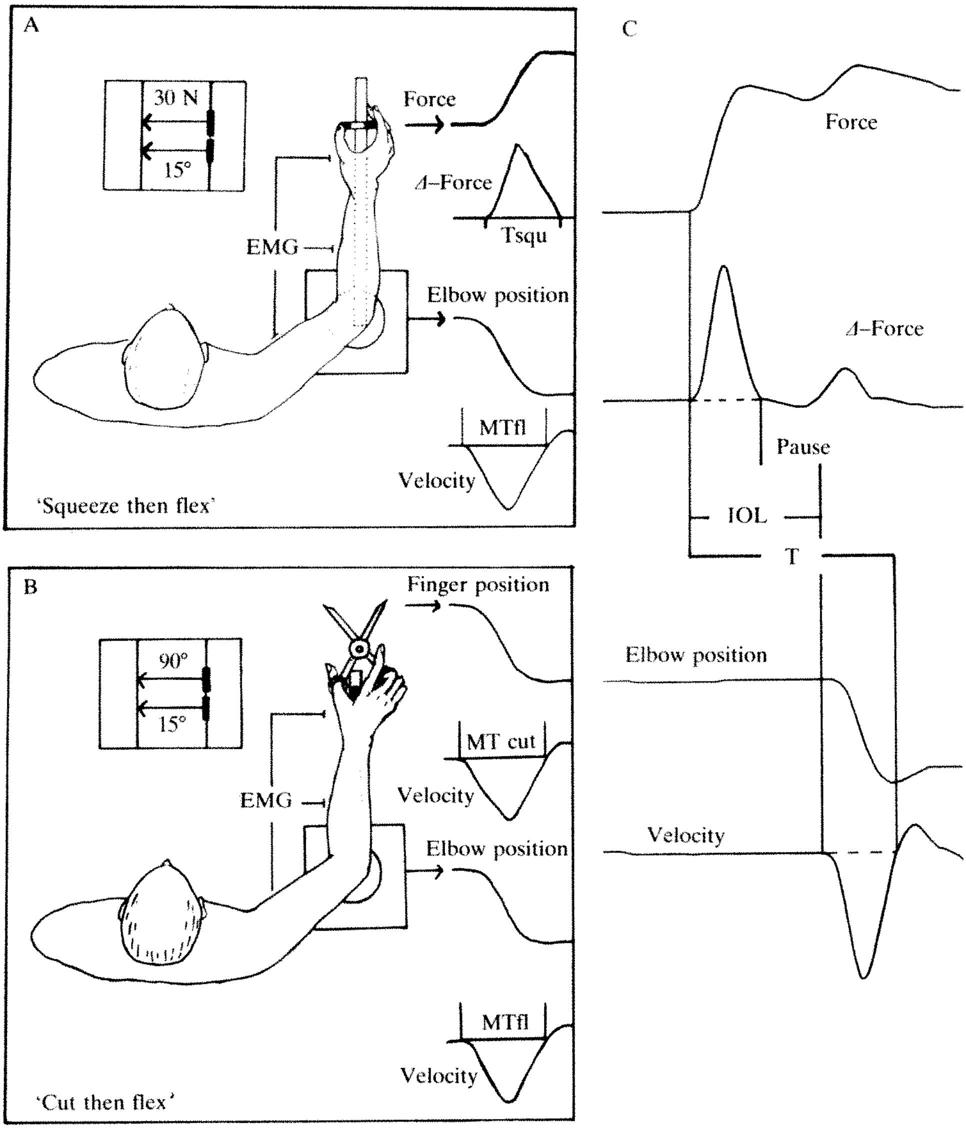

FIG. 1. Illustration of the experimental arrangements and measurements of movement performance. A, the unilateral 'squeeze then flex' task. Subjects were asked to perform an isometric opposition of thumb to fingers to exert a force of 30 N ('squeeze') and immediately after this target was reached to initiate an elbow flexion over an angle of 15° ('flex'). Both movements had to be performed as fast as possible. Fixed starting and target positions (1 cm apart) as well as the movement responses were displayed as vertical bars on an oscilloscope screen 60 cm before the subject. Movement times (Tsqu, MTfl) were measured from records of Δ-force (first derivative of the force signal) and velocity of 'flex' (onset to zero crossing). B, the unilateral 'cut then flex' task. Subjects were asked to perform an isotonic opposition of thumb to fingers ('cut') from a starting angle of 135° (between the scissor arms) to an angle of 45° and then to flex the elbow joint (15°). The movement times (MT cut, MTfl) were measured from the velocity signals. C, the measurements of timing in a sequential movement (e.g., 'squeeze then flex' task). Total movement time (T) was measured from onset of the first movement to end of the second movement. The interonset latency (IOL) was the time between the onsets of both movements. The pause was the time between termination of the first to onset of the second movement.

A weight equivalent to that of the force transducer (350 g) was added to the end of the manipulandum on the right side in order to maintain a constant inertia of the manipulandum.

'Cut then flex' task. For measurements of an isotonic opposition of thumb and finger ('cut'), a vertical rod was attached to the manipulandum so that it was positioned between the thumb and the index finger of the pronated arm. The thumb and the middle finger were placed in the arms of a pair of scissors; the intersection of the arms of the scissors was connected to a potentiometer. Subjects were asked to perform a 'cut' movement of 90° from a starting angle of 135° (between the scissor arms) to an angle of 45° (*see* fig. 1B).

'Flex then squeeze' task. This task resembled that of unilateral 'squeeze then flex' with the exception that the sequence of the movements was reversed.

Recordings and Data Analysis

Separate movements and the sequential movements of each task were performed in a cyclical order. Each individual performed 5 practice trials of each of the separate movements and of the sequential movement; thereafter 10 single trials of each type of movement were collected.

Electromyographic (EMG) activity was recorded with surface electrodes over the right biceps brachii, triceps brachii and either the right or the left opponens pollicis. Joint positions, joint velocities (electronically derived from the joint position signals), force and its first derivative (Δ-force), and the rectified EMG signals were recorded by a PDP 12 computer with a sampling rate of 250 Hz per channel using programs devised by Mr H. B. Morton. The EMG signals were preamplified (Devices 3160 with a time constant of 60 ms, low pass filtered to attenuate the signal by 3 dB at 2.5 kHz), then amplified (Devices 3120 amplifier) and processed by modules designed by Mr H. C. Bertoya.

Measurements were made on each single trial using the computer display unit. Durations of 'flex' and 'cut' were measured by visual inspection of the velocity signals (from onset to the first zero-crossing (fig. 1)). Force rise time during 'squeeze' was measured by means of Δ-force (fig. 1A). In sequential movements the interonset latency (IOL) was measured from velocity or Δ-force onset of the first movement to onset of the second movement. Total movement time for a sequential movement (T) was measured from onset of the first movement to termination of the second movement (fig. 1C).

Student's t test (paired or unpaired as appropriate) was used for comparison of inter and intra-individual analyses of the data. Linear correlation coefficients were used to assess the relationships between movement times in the sequential tasks. Spearman's test of rank correlation was used to test the relation between clinical akinesia scores and the parameters of sequential movements.

Reaction times were measured from the go-signal to movement onset (velocity for 'flex'; Δ-force for 'squeeze'). Excessively short ($<$ 100 ms) or long ($>$ 1.5 times the mean) response times were not included in calculation of the mean values presented in Table 2.

RESULTS

Unilateral 'Squeeze then Flex' Task

This task was performed in all 10 patients and the 9 normal controls. Fig. 2 shows the performance of a unilateral sequential 'squeeze then flex' task in a patient with Parkinson's disease, compared with a normal subject. The data from all 10 patients are summarized in Table 1. The separate movement times of 'flex' (349 vs 229 ms) and 'squeeze' (221 vs 156 ms) were slower in the patients than in normal subjects ($P < 0.001$ for both 'flex' and 'squeeze'). The mean movement times in the patients for 'flex' (MTfl) and 'squeeze' (Tsqu) were longer in the sequential than in the separate performance. Tsqu (first movement of the sequence) increased from 221 to 254 ms ($P < 0.01$). The increase of MTfl (second movement

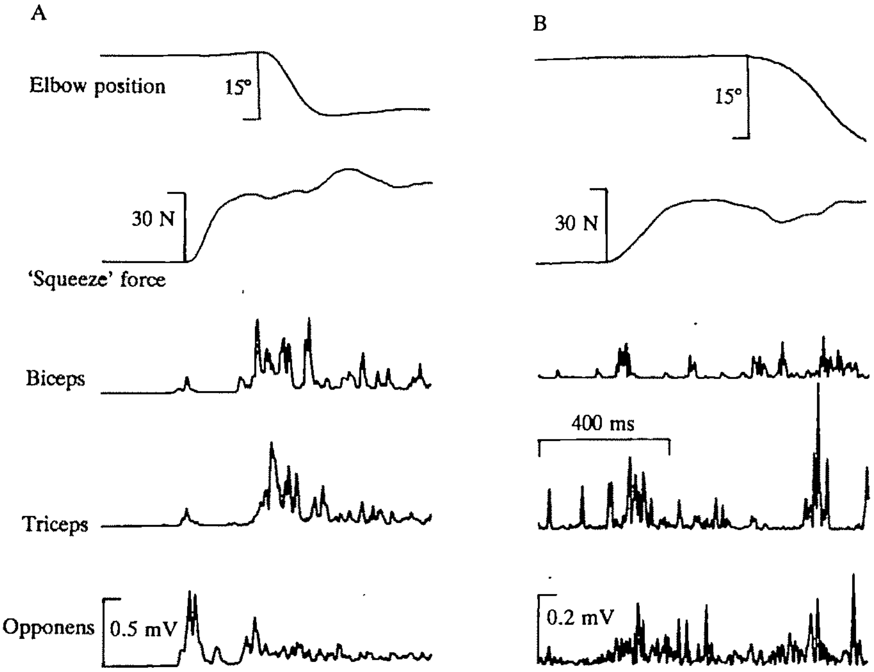

FIG. 2. Performance of a unilateral 'squeeze then flex' task in a representative normal subject (A) and a patient with Parkinson's disease (B). A and B show single trials. Traces are (from top to bottom) elbow position ('flex') force ('squeeze') and rectified EMG signals (remaining traces). Calibrations for EMG signals at bottom traces apply to all muscles. Time calibration in B applies to A and B. Note the slower movement times and the prolonged IOL in the patient (*Case 2*; *see* Table 2).

of the sequence) was even more pronounced (from 349 to 445 ms; $P < 0.001$). This was not the case in normal subjects (Tsqu for 'squeeze' 156 vs 150 ms, MTfl for 'flex' 229 vs 244 ms, $P > 0.05$).

The execution and timing of the two sequential movements was disturbed in patients with Parkinson's disease. The patients found it difficult to learn the sequential task during the practice runs. Having learned the task, the mean interonset latency was prolonged when compared with that in normal subjects (425 vs 244 ms, $P < 0.001$). The prolonged interonset latency between the two components of the task was not simply the result of the slowed first movement (Tsqu); the pause between both movements of the sequence was prolonged. In normal subjects the mean pause (IOL minus Tsqu) was 94 ms, in patients with Parkinson's disease the duration of the pause was 171 ms ($P < 0.01$). As a result of the prolonged interonset latency and movement time for 'flex' the total movement time (T) for the sequential movement was strikingly prolonged (870 vs 488 ms, $P < 0.001$). It was unlikely that, in patients with Parkinson's disease, the second movement was delayed as a result of a slow response to an internal trigger (e.g., onset of squeeze) since the simple visual reaction time for 'flex' was only slightly and not significantly, longer than in normal subjects (195 ms, normals, vs 218 ms, patients; $P > 0.05$).

Movement times for 'squeeze' and 'flex' as well as the duration of the pause between the movements, varied somewhat from trial to trial in each patient. However, when a series of 10 individual trials in each patient was analysed, there was no fixed time relationship between movement times and the pause (Tsqu vs pause: average correlation coefficient, $r = 0.21 \pm 0.4$, $P > 0.05$; pause vs MTfl: average correlation coefficient $r = -0.32 \pm 0.3$, $P > 0.05$; Tsqu versus MTfl: average correlation coefficient $r = 0.12 \pm 0.4$, $P > 0.05$). The same was true in the normal subjects (*see* Benecke *et al.*, 1986*b*).

TABLE 1. MOVEMENT PERFORMANCE IN THE UNILATERAL 'SQUEEZE THEN FLEX' TASK

	Separately[a]		*Sequentially*[b]				
Case	*Tsqu* (*ms*)	*MTfl* (*ms*)	*Tsqu* (*ms*)	*MTfl* (*ms*)	*IOL*[c] (*ms*)	*T*[d] (*ms*)	*sRT*[e] (*ms*)
1 (J.M.)	255 (51)[f]	347 (47)[f]	284 (47)	490 (62)	455 (83)	945 (82)	247 (12)
2 (W.R.)	243 (31)	323 (45)	276 (7)	412 (84)	440 (84)	852 (79)	220 (24)
3 (H.S.)	177 (18)	360 (21)	213 (20)	390 (34)	354 (38)	744 (62)	166 (7)
4 (A.R.)	260 (87)	497 (82)	255 (31)	627 (184)	515 (89)	1142 (98)	260 (25)
5 (M.C.)	198 (22)	301 (44)	238 (31)	374 (48)	418 (81)	792 (79)	183 (19)
6 (R.C.)	193 (19)	267 (37)	198 (28)	343 (31)	389 (74)	732 (59)	270 (21)
7 (A.G.)	230 (30)	479 (15)	270 (37)	658 (55)	446 (73)	1104 (81)	199 (7)
8 (A.B.)	212 (38)	296 (36)	259 (34)	380 (33)	388 (71)	768 (61)	180 (10)
9 (A.S.)	246 (48)	300 (26)	327 (54)	398 (46)	445 (64)	843 (69)	212 (13)
10 (W.W.)	194 (7)	324 (30)	219 (35)	387 (41)	391 (71)	778 (71)	244 (21)
Mean (SD)+	221 (29)	349 (77)	254 (38)	445 (110)	425 (46)	870 (147)	218 (34)
Mean (SD)+ controls	156*** (23)	229*** (41)	150*** (25)	244*** (35)	244*** (33)	488*** (42)	195 (12)

Measurements of 10 patients with Parkinson's disease (mean age 58±10 yrs) and 9 age-matched controls (mean age 47±16 yrs). [a] Separately = measurement of movement times for isometric 'squeeze' (Tsqu) and elbow 'flex' (MTfl) when executed separately. [b] Sequentially = measurement of movement times in the sequential task of 'squeeze then flex'. [c] IOL = interonset latency; time from onset of 'squeeze' to onset of 'flex'. [d] T = total movement time; time from onset of 'squeeze' to termination of 'flex'. [e] sRT = simple reaction time for 'flex'. [f] Mean value (±SD) of 10 consecutive trials. + Mean of the mean values obtained in each subject. Stars indicate differences between normal subjects and patients with Parkinson's disease (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$).

When patients were asked to modify voluntarily the interonset latency between the 'squeeze' and the 'flex', surprisingly the majority (n = 7) were unable to perform this task satisfactorily. They either performed both movements simultaneously, or used the timing strategy employed previously with the normal instruction. Only in 3 patients (Cases 5, 6, 10) could a considerable number of trials with either short or long interonset latencies be obtained. The most striking finding in these 3 subjects was of an inverse relationship between interonset latency and the time taken to perform the flexion movement at interonset latencies less than about 400 ms, that is, the shorter the interonset latency, the longer the time taken to flex the elbow and the lower its velocity. At long interonset latencies the movement times

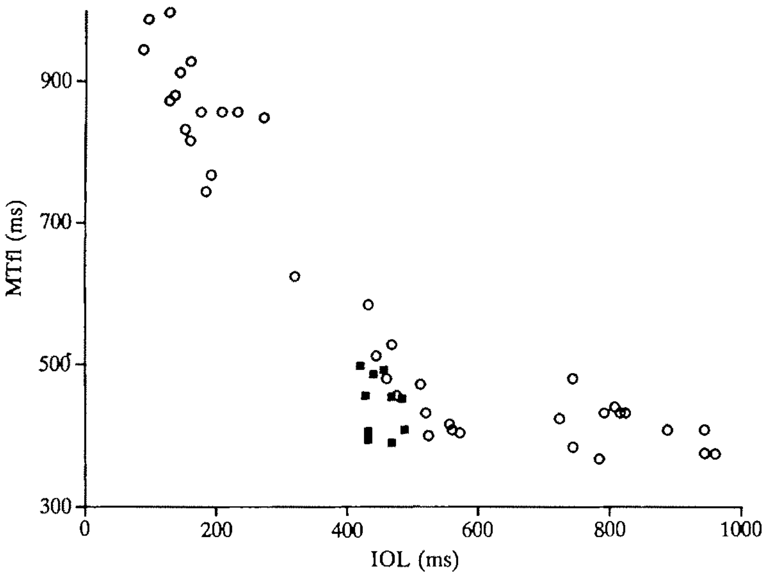

FIG. 3. Relationship between interonset latency (IOL) and duration of the second movement (MTfl) in a patient with Parkinson's disease (*Case 5*). Unilateral 'squeeze then flex' task. First, the patient performed the task with the normal instruction (solid squares). Then he was asked to modify voluntarily the IOL between the two movements (open circles). Note the prolonged movement times at IOLs < 400 ms ('refractory period' of movement speed production). When the patient followed the normal instruction, he automatically chose an IOL which enabled him to perform relatively rapid second movements.

remained fairly constant (fig. 3). For the shortest interonset latencies the velocity signals usually exhibited a double peak (fig. 4). When patients followed the normal instruction to 'squeeze' and then 'flex' as fast as possible, they automatically chose interonset latencies which enabled them to perform the second movements at almost maximum speed with relatively short interonset latencies. It should be noted that the speed of flexion during the sequential task, in the patient illustrated in fig. 4, never quite reached the maximum (i.e., 301 ms) seen when the elbow flexion was performed on its own, even with interonset latencies of greater than 800 ms. The results obtained in all 3 patients who could be analysed in this experiment showed similar findings.

Bilateral 'Squeeze then Flex' Task

This task was performed in 5 patients and in 5 normal controls. Fig. 5 shows representative performance in the bilateral sequential 'squeeze' (left arm) then 'flex' (right arm) task in a patient with Parkinson's disease and in a normal subject. The data from all patients are summarized in Table 2. As in the unilateral 'squeeze then flex' task, movement times for the second 'flex' were longer in the bilateral sequential task than in the separate performance in the patients (MTfl; 371 vs 338 ms, $P < 0.01$). Movement times for the first ('squeeze') task were unchanged (216

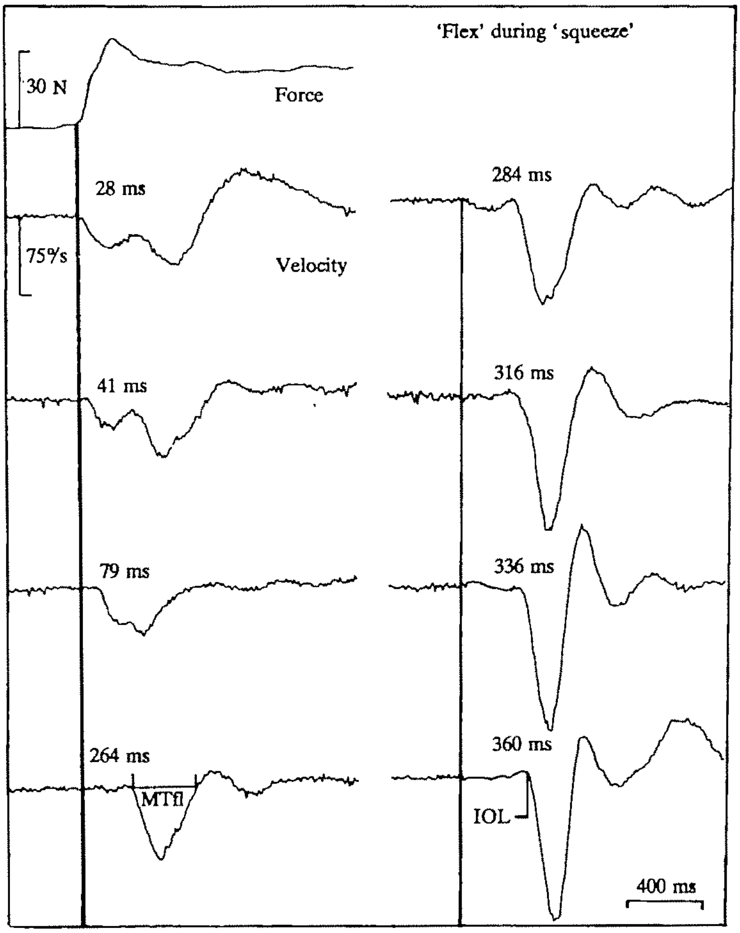

FIG. 4. Velocity profiles of the second movement ('flex') in the unilateral 'squeeze then flex' task in a patient with Parkinson's disease (*Case 6*). The patient was asked to modify voluntarily the interonset latency (IOL) between the two movements, so that the 'flex' began at different times after the start of 'squeeze'. Traces are averaged ($n = 8$) force signal of 'squeeze' (*top*), and velocity signals (single trials) (remaining traces) of elbow 'flex' initiated at increasing IOLs (*see* figures next to each trial, from top to bottom and left to right). Calibration at first velocity signal applies to all following traces. Time calibration applies to all traces. Note the double-shaped velocity signals and the decreased peak amplitudes of the 'flex' at short IOLs.

vs 190 ms; $P > 0.05$). The interonset latency in the bilateral task was strikingly prolonged in the patients as compared with normals (380 vs 226 ms; $P < 0.001$).

Unilateral 'Cut then Flex' Task

This task was performed in 5 patients and in 5 normal subjects. Fig. 6 shows representative performances in this task in a normal subject and a patient. The movement parameters of all patients are summarized in Table 3. Simple isotonic finger flexion ('cut') was slower in patients with Parkinson's disease than in normals (197 vs 160 ms, $P < 0.001$). In the sequential task the movement time for 'flex'

TABLE 2. MOVEMENT PERFORMANCE IN THE BILATERAL 'SQUEEZE THEN FLEX' TASK

	Separately[a]		*Sequentially*[b]		
Case	*Tsqu* (*ms*)	*MTfl* (*ms*)	*Tsqu* (*ms*)	*MTfl* (*ms*)	*IOL*[c] (*ms*)
3	188 (15)	361 (27)[f]	208 (21)	402 (22)	334 (38)
5	196 (21)	315 (38)	229 (29)	348 (28)	398 (61)
6	184 (33)	274 (29)	195 (24)	299 (19)	348 (51)
7	180 (13)	405 (49)	240 (33)	448 (41)	410 (46)
10	204 (19)	336 (52)	208 (28)	356 (38)	409 (61)
Mean (SD)+	190 (10)	338 (49)	216 (18)	371 (57)	380 (36)
Mean (SD)+ controls	164* (21)	244** (47)	168** (20)	252** (48)	226*** (23)

Measurements of 5 patients with Parkinson's disease (mean age 64.4 ± 8 (SD) yrs) and 5 age-matched controls (mean age 52.6 ± 12 yrs). For further explanations, *see* footnote to Table 1.

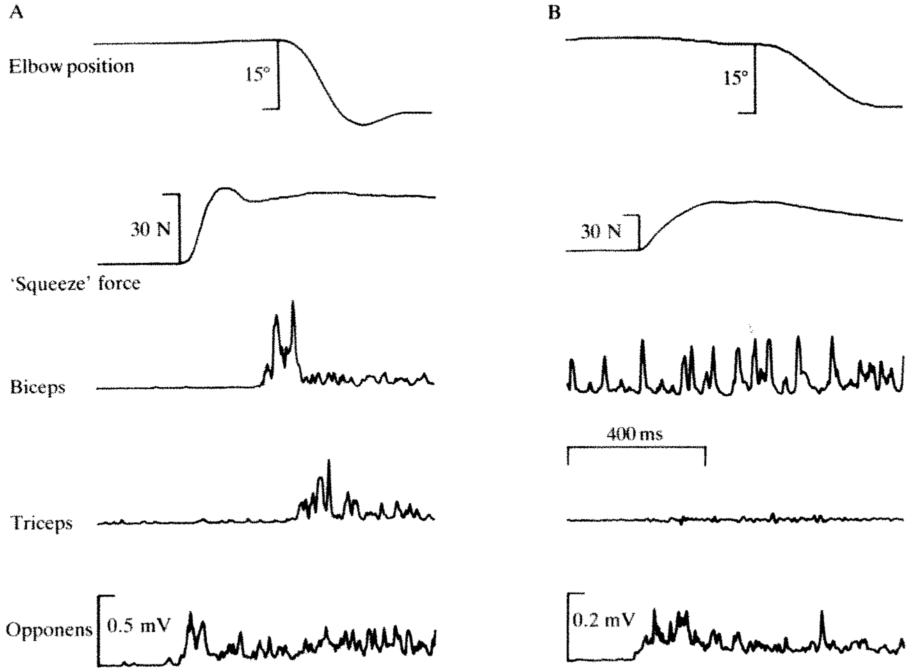

FIG. 5. Performance of a bilateral 'squeeze then flex' task in a representative normal subject (A) and a patient with Parkinson's disease (*Case 5*) (B). The subjects were asked to 'squeeze' with the left arm then 'flex' with the right arm. A and B show single trials. For further explanations, *see* legend of fig. 2. Note the increased interonset latency and the prolonged movement times for both 'squeeze' and 'flex' in the patient.

(MTfl) was slower than in the separate movement in patients (347 vs 311 ms, $P < 0.05$) but not in normals (176 vs 177 ms). The time taken to perform the 'cut' movement (MT cut) was the same whether executed separately or simultaneously in both patients and normals ($P > 0.05$). Interonset latencies were strikingly prolonged in the patients with Parkinson's disease as compared with normals (397 vs 231 ms; $P < 0.001$).

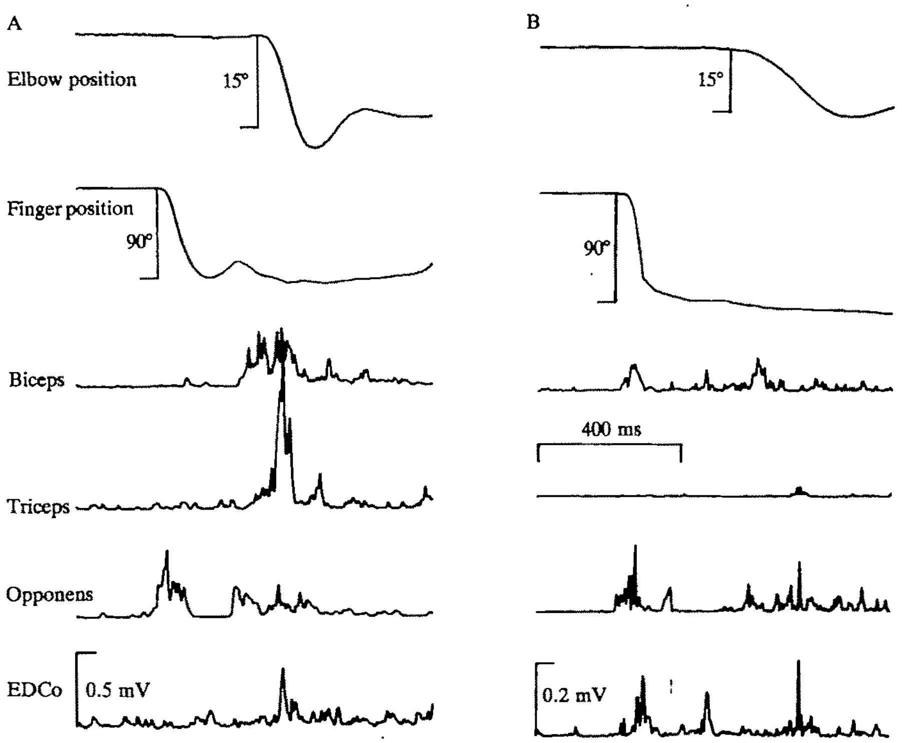

FIG. 6. Performance of a unilateral 'cut then flex' task in a representative normal subject (A) and a patient with Parkinson's disease (*Case 5*) (B). A and B show single trials. For further explanation, *see* legend of fig. 2. Note the prolonged IOL and the slower 'flex' in the patient. EDCo = extensor digitorum communis.

Unilateral 'Flex then Squeeze' Task

This task was performed in 5 patients and in 5 normal subjects. The results are presented in Table 4. In normal subjects, the first movement ('flex') in this sequential task was considerably longer than the initial 'squeeze' or 'cut' in the other tasks (235 vs 150 or 157 ms, respectively). The duration of 'flex' lay in the same region as the 'optimal' interonset latency for sequencing movements (around 200 ms). For this reason it was to be expected that the second movement ('squeeze') in the 'flex then squeeze' task would be initiated immediately after termination of the first ('flex'), rather than with a considerable pause between them. As can be seen from Table 4, this was the case in normal subjects; the mean duration of 'flex' in

TABLE 3. MOVEMENT PERFORMANCE IN THE UNILATERAL 'CUT THEN FLEX' TASK

	Separately[a]		*Sequentially*[b]		
Case	*MTcut* (*ms*)	*MTfl* (*ms*)	*MTcut* (*ms*)	*MTfl* (*ms*)	*IOL*[c] (*ms*)
5	184 (12)[f]	317 (32)	191 (23)	384 (29)	363 (44)
6	194 (14)	282 (28)	201 (21)	302 (27)	368 (39)
8	202 (15)	302 (50)	244 (33)	344 (42)	424 (52)
9	217 (19)	304 (44)	218 (22)	324 (38)	444 (54)
10	192 (16)	352 (32)	229 (18)	383 (25)	388 (46)
Mean (SD)[+]	197 (11)	311 (26)	217 (21)	347 (36)	397 (35)
Mean (SD)[+] controls	160*** (8)	177*** (37)	157*** (10)	176*** (41)	231*** (24)

Measurements of 5 patients with Parkinson's disease (mean age 59.4 ± 10 (SD) yrs) and of 5 age-matched controls (mean age 52.2 ± 18 yrs). For further explanations, *see* footnote to Table 1.

the sequence was 235 ms and the mean interonset latency was 246 ms. Thus there was little pause between termination of 'flex' and onset of 'squeeze'.

Movement times for 'flex' varied from trial to trial, so the question arose as to whether the onset of the second ('squeeze') movement was exactly adjusted to the end of the foregoing 'flex' in each individual sequential movement. However, MTfl and interonset latency were not closely related in 10 consecutive trials in each normal subject (average correlation coefficient, $r = 0.42$, $P > 0.05$).

In the patients with Parkinson's disease there was an additional slowness of both movements in the sequence as compared with movement times when they were executed separately (Table 4). MTfl increased from 352 to 472 ms ($P < 0.01$); Tsqu increased from 229 to 243 ms ($P < 0.05$). When the mean movement times in any

TABLE 4. MOVEMENT PERFORMANCE IN THE UNILATERAL 'FLEX THEN SQUEEZE' TASK

	Separately[a]		*Sequentially*[b]		
Case	*MTfl* (*ms*)	*Tsqu* (*ms*)	*MTfl* (*ms*)	*Tsqu* (*ms*)	*IOL*[c] (*ms*)
1	347 (47)[f]	255 (51)	496 (55)	257 (30)	522 (41)
2	323 (17)	243 (31)	385 (44)	263 (20)	417 (44)
4	497 (82)	260 (87)	612 (69)	283 (23)	632 (41)
6	267 (37)	193 (19)	382 (41)	201 (31)	415 (40)
10	324 (30)	194 (7)	487 (35)	211 (18)	512 (51)
Mean (SD)[+]	352 (86)	229 (33)	472 (95)	243 (36)	500 (90)
Mean (SD)[+] controls	229* (41)	156** (23)	235** (37)	164** (25)	246*** (43)

Measurements of 5 patients with Parkinson's disease (mean age 56.6 ± 14 (SD) yrs) and of 5 age-matched controls (mean age 47.0 ± 16 yrs). For further explanations, *see* footnote to Table 1.

one patient or the mean values of all patients for 'flex' (MTfl) in the sequence were compared with the interonset latencies it became clear that, as in normal subjects, the onset of the second movement ('squeeze') could be adjusted appropriately to the termination of 'flex' (the mean duration of 'flex' was 472 ms, and the mean interonset latency was 500 ms). As in normal subjects, however, the interonset latency in single trials was not significantly correlated with the duration of the foregoing 'flex' (average correlation coefficient, $r = 0.44 \pm 11, P > 0.05$).

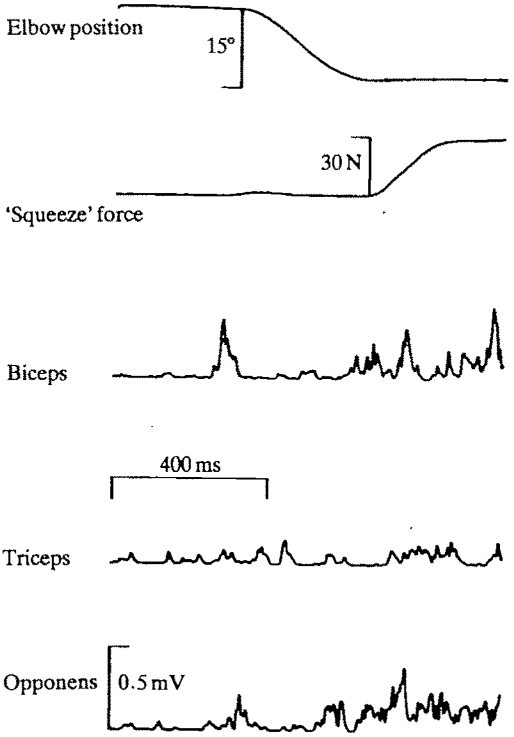

FIG. 7. Adjustment of timing of 'squeeze' in a 'flex then squeeze' task in a patient with Parkinson's disease (*Case 6*). The patient was asked to execute both movements at maximal speed without any pause between them (normal instruction). Traces are elbow position (*top*), force (*second from top*), and rectified EMG signals (remaining traces). Calibration of EMG amplitude (*bottom trace*) applies to all EMG recordings. Time calibration is for all traces. Note that the 'squeeze' starts immediately after termination of 'flex', even though the latter is very slow.

The interonset latencies in this task were considerably longer than those measured in the other tasks (compare values of Table 4 with those of Tables 1, 2 and 3), which indicated that the patients did not simply use a stereotyped timing for all rapid sequential movements. Fig. 7 gives a representative example of the appropriate timing of the second movement ('squeeze') with an onset just after termination of 'flex' in a patient with Parkinson's disease.

Relation between Movement Times and Akinesia

Total movement time (T) and interonset latency in the unilateral 'squeeze then flex' task were correlated with the degree of clinically-established akinesia (fig. 8) ($P < 0.025$), and with one objective measure of akinesia the (pegboard test ($P < 0.05$), but not with the other, the two-point touching test ($P > 0.05$).

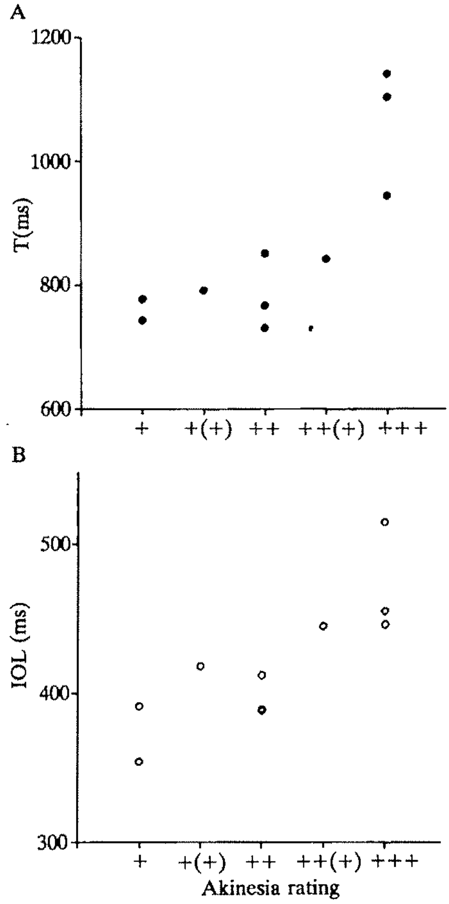

FIG. 8. Relation between the degree of akinesia evaluated clinically and movement times in the unilateral 'squeeze then flex' task for 10 patients with Parkinson's disease. A shows the values of total movement time (T). B shows the interonset latencies (IOL). Each circle shows the mean of 10 consecutive movements in an individual patient. In B the values of *Cases 6 and 8* are superimposed (lower circle at ++). Both total movement time (T) and interonset latency (IOL) were significantly correlated with the degree of akinesia.

DISCUSSION

Motor Programs and Motor Plans

It is convenient to discuss the implications of the present findings in terms of motor programs and motor plans. We envisage a motor program as a set of rules for executing a movement in which the muscles to be used (i.e., agonists, antagonists, synergists and fixators) and the timing of their actions are predictably related. For a movement of given amplitude and speed, the rules of the program specify the relative activity in each muscle and the exact timing between them. A single rapid movement at one joint employs a single program, evident in the EMG as the well-known triphasic burst pattern of agonist, antagonist and agonist muscles. Some more complex tasks involving a series of movements at several joints also are controlled by a single motor program. This conclusion is based on the observation that there is a fixed relationship between the amplitude and velocity of the individual motor steps composing the whole movement. Constant spatiotemporal patterns between movement steps have been observed for locomotion (Shapiro *et al.*, 1981), learned sequential forearm movements (Carter and Shapiro, 1984), handwriting (Denier van der Gon and Thuring, 1965), typewriting (Terzuolo and Viviani, 1980) and speech articulation (Tuller *et al.*, 1982). However, some complex movements are not governed by a single generalized motor program. As we have argued before (Benecke *et al.*, 1986*b*), certain sequential combinations of two movements, such as the 'squeeze and flex' or 'cut and flex' tasks in the present experiments, are executed by running two separate motor programs one after the other. The reason for saying this is that there is no correlation between the times taken to perform the two components of the task as would be the case were the movement governed by a single complex motor program (Carter and Shapiro, 1984). Thus it is not possible to predict the timing of the second movement from inspection of the first. Hence there must be one set of rules controlling the execution of the first movement and another set for the second. It is these sets of rules which we refer to as motor programs. The combination of motor programs required to carry out a complex motor act can be termed a motor plan. Part of the function of the motor plan would be to time the onset of the individual programs which make up the total movement.

Extra Slowness of Complex Movements in Parkinson's Disease

Simple single rapid limb movements in patients with Parkinson's disease are slower than in normal subjects (Draper and Johns, 1964; Flowers, 1976; Hallett and Khoshbin, 1980; Berardelli *et al.*, 1986; Benecke *et al.*, 1986*a*), but the degree of slowing in the performance of simple movements is often not closely related to the degree of clinical akinesia (Benecke *et al.*, 1986*a*; Berardelli *et al.*, 1986). Greater disturbances of movement, and a closer relation with akinesia, were found for simultaneous movements (Benecke *et al.*, 1986*a*). When patients were asked to initiate an elbow flexion and an isometric finger grip at the same time, both movements were dramatically slower compared with their speed when executed individually. The same has been found for sequential movements in the present study. We refer to simultaneous or sequential combinations of two or more simple movements as complex movements. Motor disturbance in Parkinson's disease appears to be more pronounced in more complex tasks. Sanes (1985) also found that decreasing target size in goal-directed movements, which made the task more difficult, exaggerated motor disturbances in patients with Parkinson's disease.

In the present investigation there were no correlations between the times taken to perform the two components of a sequential movement, so it is suggested that each movement is governed by its own program. Running of two motor programs in a sequence clearly was disturbed in patients with Parkinson's disease compared with normals. The mean movement time to complete, for example, the unilateral 'squeeze then flex' task amounted to 870 ± 147 ms in patients with Parkinson's disease, whereas normal subjects completed this task in 488 ± 42 ms (*see* Table 1). The extra slowness in executing such complex motor sequences was closely related to the degree of clinically evaluated akinesia.

Why are Motor Sequences Slowed in Parkinson's Disease?

The question arises as to whether motor sequences are slow because the two movements are reduced in speed and/or because the time to switch from one program to another is prolonged. As far as the 'squeeze then flex' and the 'cut then flex' tasks are concerned, both factors contributed to the prolongation of total movement time. (The 'flex then squeeze' task is discussed later.)

In patients with Parkinson's disease, the second movement of a sequence was always slower than when it was performed separately. Indeed, in the unilateral 'squeeze then flex' task, even the first movement had a reduced velocity. In addition, the interval between the two movements in a sequence was disturbed in the patients with Parkinson's disease. First, on occasion some patients found it difficult to switch from one movement to the next. Second, when they achieved the sequence they did so, on average, with a prolonged interonset latency. Part of this increase in interonset latency may have been caused by the slowness of the patients' first movement. However, this was not the only factor. The pause between the end of the first movement and the onset of the second also was prolonged.

It is not immediately clear why the second movement of a sequence was slower than usual in the patients. In normal subjects it has been shown that the second movement of a sequence achieves maximal speed only when there is a delay of about 230 ms between the onsets of the first and second movements (Benecke *et al.*, 1986*b*). If the second movement of a sequence is initiated less than 200 ms after the first, it can no longer be performed at maximal speed. The present investigation shows that this 'refractory period' is prolonged in patients with Parkinson's disease up to about 400 to 500 ms. As in the normal group when patients attempted voluntarily to make movements at shorter interonset latencies, the second movement was very much slower. Although this was the normal timing that the patients chose for their interonset latencies, the speed of the second movement of the sequence was still not quite maximal. Two factors contributed to the slowness of the second movement. First, many patients performed the sequence with variable interonset latencies, some of which were less than 400 ms. It follows that such movements were likely to be slow, thereby contributing to the average extra slowness of the second movement. Second, in the 3 patients who could change their interonset latencies voluntarily, maximal speed was never quite achieved, even with latencies greater than 500 ms. A very long period of recovery may be needed in patients with Parkinson's disease before movement speed recovers fully.

These deficits in sequencing two simple movements might be exacerbated if more than two movements have to be performed. The third movement of a long sequence might be even slower, and have an even longer interonset latency than the second, and likewise for additional movements. If so, this type of mechanism might explain the breakdown of repetitive movements in patients with Parkinson's disease (Wilson, 1925; Schwab *et al.*, 1959). Schwab and colleagues (1959) may have had a similar idea in mind when they described the phenomenon as 'central myasthenia'.

These various disturbances in organization of a sequence of movements in patients with Parkinson's disease imply a difficulty in organizing a motor plan; there is difficulty in switching from one movement to the next.

The 'Flex then Squeeze' Task

In the previous tasks of 'squeeze then flex' (unilateral or bilateral), the interonset latency appeared to be fixed at the minimum possible interval. This meant that there was a pause between the end of a rapid squeeze and the start of the subsequent movement. Analysis of the 'flex then squeeze' task allows us to investigate a rather different aspect of motor control. In this task, the duration of the 'flexion' movement was about the same, or longer than the usual interonset latency, so that in order to start the second movement immediately after the first, subjects had to know how long the first movement might last.

This provides an opportunity for investigating the mechanisms responsible for timing the onset of the second program in a sequence. In normal subjects we have shown previously (Benecke *et al.*, 1986*b*) that if large amplitude elbow flexion movements are made, which take longer to complete than the minimum interonset latency, then the interonset latency increases to be appropriate to the duration of the first movement. The present experiments show that this also applies to patients with Parkinson's disease. In these patients, the duration of 'flex' was slightly longer then their minimum interonset latency. However, their interonset latency increased to accommodate the long duration of the 'flexion' movement in the 'flex then squeeze' task.

We conclude that despite their difficulties in running the individual component programs of a sequence, the overall timing mechanism was intact in patients with Parkinson's disease. However, we do not know what mechanism is used, either in patients or normals, to achieve this timing. There are two main possibilities: (1) the motor plan may time the whole sequence to take into account the average duration of the first movement; or (2) feedback information from the periphery or from corollary discharge during execution of the first movement may help to time the onset of the second. In the present experiments, we found no relationship between the duration of the first ('flex') movement and the latency of the second ('squeeze'). We would thus favour the first possibility but, as this evidence is not conclusive, for the present the case must remain open.

Disturbed Processing in the Supplementary Motor Area

The present investigation has shown that a bilateral sequential movement ('squeeze' with the left hand and then 'flex' the right elbow joint) was equally disturbed in Parkinson's disease as the corresponding unilateral sequential task. This finding implies that Parkinson's disease affects a bilaterally organized system which provides the coordination of bimanual motor skills. Brinkman (1981, 1984) has noted that primates with unilateral lesions of the supplementary motor area have difficulties with bimanual coordination tasks. The work of Roland and colleagues (Roland *et al.*, 1980) suggests that during execution of unilateral manual motor sequences, there are equivalent increases of regional cerebral blood flow in both supplementary motor areas. On the basis of these findings it can be suggested that the supplementary motor area plays an important role in the processing of sequential unilateral and bilateral motor skills.

Schell and Strick (1984) have shown that the supplementary motor area receives thalamic afferents most densely from nucleus VLo, which is the area of the thalamus receiving projections almost exclusively from the main output of the basal ganglia, the globus pallidus. It is probable that the deficit in the nigrostriatal dopamine system of parkinsonian patients is transferred to the supplementary motor area resulting in disturbance of unilateral and bilateral manual motor sequences.

When patients perform sequential movements, not only are the individual movements slower than normal, but the interval between movements is prolonged, and sometimes the switch from the first to the second movement cannot be made. These findings suggest that the striopallidal deficit induced by nigrostriatal dopamine deficiency in Parkinson's disease impairs the capacity to switch from one program to another in a sequence. In other words, Parkinson's disease impairs the ability to organize a motor plan. Our hypothesis is that this process normally is organized at the level of the supplementary motor cortex, guided by basal ganglia input.

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PURE WORD DEAFNESS FOLLOWING BILATERAL LESIONS

A PSYCHOPHYSICAL ANALYSIS

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SUMMARY

A detailed clinical and psychophysical study of a woman who had developed pure word deafness associated with amusia after bilateral temporoparietal destructions is reported. The patient had a defect in temporal resolution encompassing auditory, visual and somatosensory modalities, but the clinical defect was limited to the auditory sphere. Auditory comprehension did not improve even if she was spoken to slowly, although marked improvement of temporal resolution was observed as the duration of a nonlinguistic sound was extended. Also, she exhibited a supramodal defect in the perception and reproduction of rhythm, which was rate-dependent. These and other findings led to the following conclusions: (1) the auditory modality is much more dependent on temporal resolution than other sensory modalities; (2) for a full understanding of the mechanism of pure word deafness, not only the defect of temporal resolution but also many other factors, for example, defective discrimination of loudness, pitch or tone duration have to be taken into consideration; and (3) rhythm sense strongly depends on a supramodal capacity of temporal resolution.

INTRODUCTION

Pure word deafness is defined as the inability to comprehend and discriminate spoken language while spontaneous speech, reading, reading comprehension and writing are preserved, and comprehension of nonverbal sounds is relatively spared. Recent experimental studies have implicated defects in auditory processing (Jerger *et al.*, 1969; Kanshepolsky *et al.*, 1973; Albert and Bear, 1974; Auerbach *et al.*, 1982), temporal resolution (Albert and Bear, 1974), phonemic discrimination (Chocholle *et al.*, 1975; Denes and Semenza, 1975; Saffran *et al.*, 1976; von Stockert, 1982) or prephonemic discrimination (Auerbach *et al.*, 1982).

We recently had the opportunity of studying a patient with pure word deafness associated with amusia and mild auditory agnosia for environmental sounds. We have analysed temporoparietal lobe functions by several psychophysical and musical studies on this patient. The relationship between temporal resolution and clinical manifestations is discussed.

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CASE REPORT

The patient, a 26-year-old right-handed Japanese woman, began to take lessons in playing the organ at the age of 6 years and the piano at the age of 15. She graduated from a junior college at the age of 20. Her past medical history was unremarkable, and she denied taking contraceptive pills.

On January 9, 1982, while watching television, she suddenly developed a right hemiparesis and her speech became garbled and incomprehensible. She was admitted to a local hospital, where initially she could produce only a few words. The number of words later gradually increased. Her spontaneous speech contained a moderate number of verbal and literal paraphasias. Verbal comprehension, repetition and reading aloud were moderately impaired; however, she was able to sing a nursery rhyme. The general impression of the admitting physician was a predominantly posterior type of aphasia. Computed tomography (CT) revealed a low-density area in the left temporoparietal region. Left carotid angiograms showed no abnormal findings. The CSF was normal. She was thought to have had a cerebral infarct and supportive treatment was given. Her hemiparesis disappeared within a few days and her aphasia improved gradually.

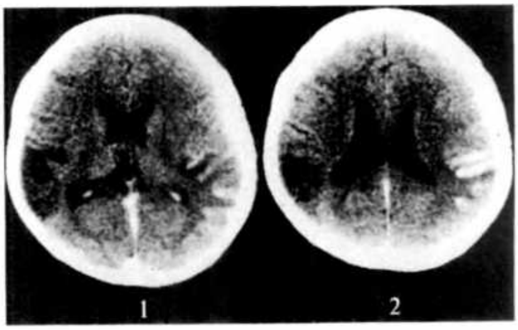


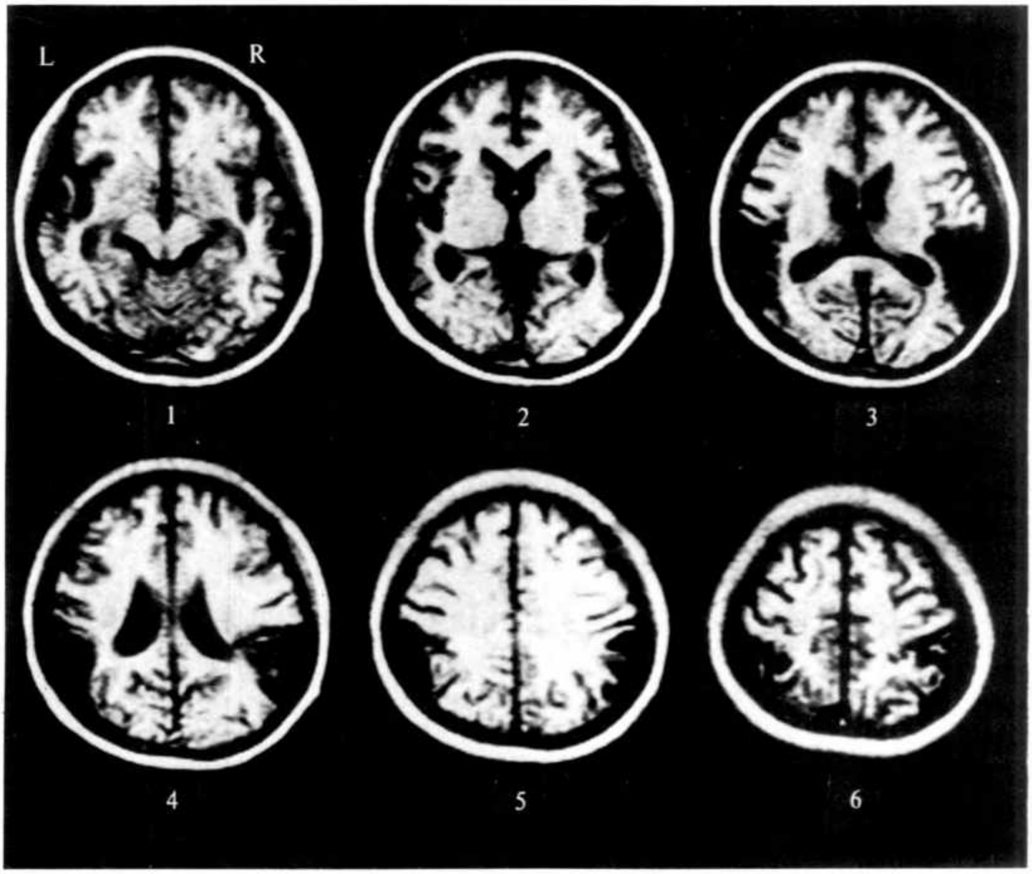
FIG. 1. CT scan of the brain after the second stroke demonstrating an enhancing lesion in the right posterior temporoparietal region and an older nonenhancing lesion in the left posterior temporoparietal region including a part of Wernicke's area.

On January 5, 1985, she suddenly had a generalized convulsion. She was at once admitted to another hospital, where she was drowsy for ten days. Thereafter, she became unable to understand spoken words, although she was able to follow written commands. The remainder of the neurological examination was normal. A CT scan demonstrated an enhancing lesion in the right posterior temporoparietal region and an older nonenhancing lesion in the left posterior temporoparietal region including a part of Wernicke's area (fig. 1). Bilateral carotid and vertebral arteriograms were normal. An EEG showed persistent theta activity in the right parieto-occipital region. She was transferred to the Neurology Service of Hyogo Brain and Heart Center at Himeji on May 1, 1985, for further examination.

On admission she was attentive, cooperative and orientated in time and place with a good insight into her illness. General physical examination revealed a normal heart rate and rhythm. Blood pressure was 120/80 mmHg in both arms. There were no carotid bruits. Remote and recent memory was intact. Calculations were done moderately well. She could identify most nonverbal sounds such as a telephone ringing or water running from a tap, but could not understand spoken words, which sounded like an echo. Visual fields were normal to confrontation, and the cranial nerves intact except for auditory function, which will be described in detail below. Findings of sensory and cerebellar tests were unremarkable. Motor examination revealed normal muscle tone without weakness. The tendon reflexes were normal bilaterally without pathological reflexes. Right-left orientation, two-point discrimination, skin graphaesthesia, point localization, finger naming, optokinetic nystagmus, visually-guided reaching, stereognosia and spatial ability were all intact. Double simultaneous stimulation (auditory, tactile and visual) was correctly perceived on both sides.

Laboratory findings were all normal, including immunology, coagulation and cardiac surveys (echocardiography and ambulatory Holter electrocardiography). An EEG, performed on May 9, 1985, was within normal limits.

Magnetic resonance imaging (MRI) with 10 mm slices, performed on May 27, 1985, revealed that the left lesion was situated in the middle and posterior portion of the superior temporal gyrus involving most of Heschl's gyrus and the geniculotemporal auditory radiation. There was another lesion in the left parietal lobe involving the supramarginal and angular gyri. The right lesion, more extensive than the left, was in the middle and posterior portion of the superior temporal gyrus and in the parietal lobe involving the supramarginal and angular gyri. Involvement of Heschl's gyrus and the auditory radiation was also more extensive on the right (figs 2, 3, 4).



FIGS 2, 3, 4. MRI performed on May 27, 1985 showing bilateral posterior temporoparietal lesions including the primary auditory area and the auditory radiation on each side, greater in the right hemisphere. Figs 2, 3, and 4 show horizontal, coronal and sagittal sections, respectively (in fig. 4, the upper figures show the left hemisphere and the lower show the right).

RESULTS

Neuropsychological Examination

Abnormally loud and dysprosodic spontaneous speech was fluent with very rare phonemic paraphasic errors. Visual confrontation naming, reading aloud, reading

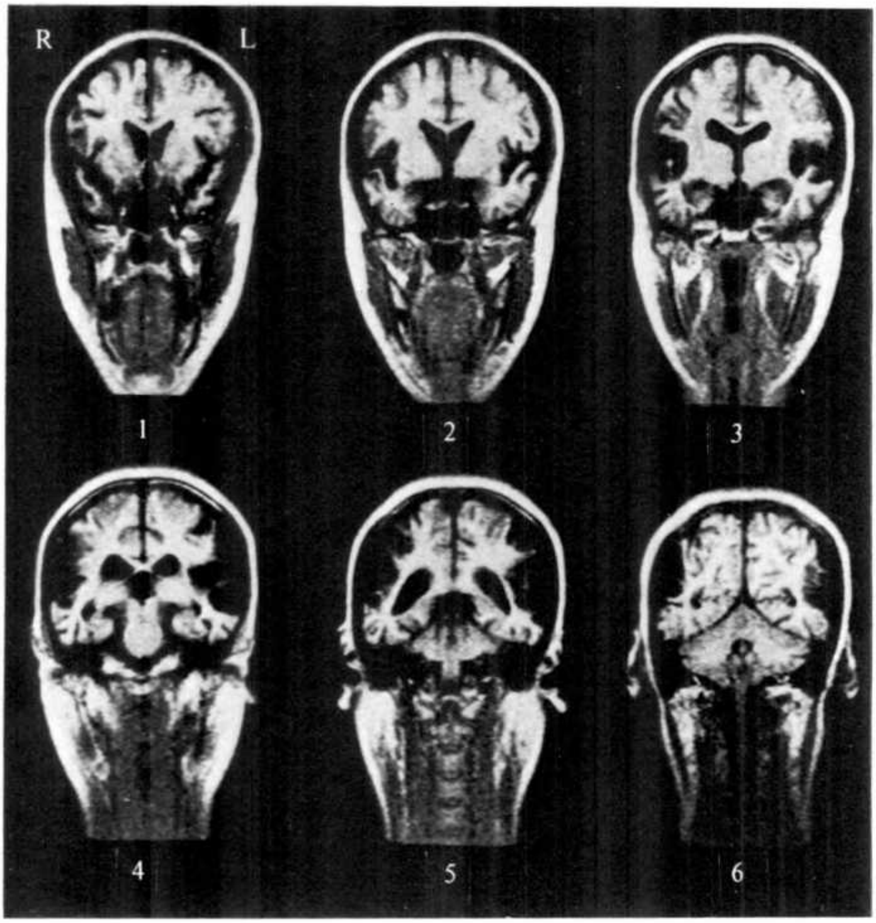


FIG. 3

comprehension and spontaneous writing were normally performed. She could correctly execute four-step written commands. Her score of the Token Test presented as written commands, performed on May 10, 1985, was 92% correct. Verbal comprehension was markedly impaired and she was unable to identify even a single word. Slowing the rate of speech by increasing the interval between syllables, or lip-reading, did not improve her comprehension. Repetition of a single word and a phrase was severely impaired. The results of the standard language test of aphasia (SLTA) (Takeda, 1977), performed on May 10, 1985, are summarized in Table 1. Praxis was normal. Copying of a cube was done well. Colour recognition and visual object recognition were normal. Her intelligence level according to WAIS, performed on May 14, 1985, was as follows: Verbal IQ = 84, Performance IQ = 91 and Whole Scale IQ = 86.

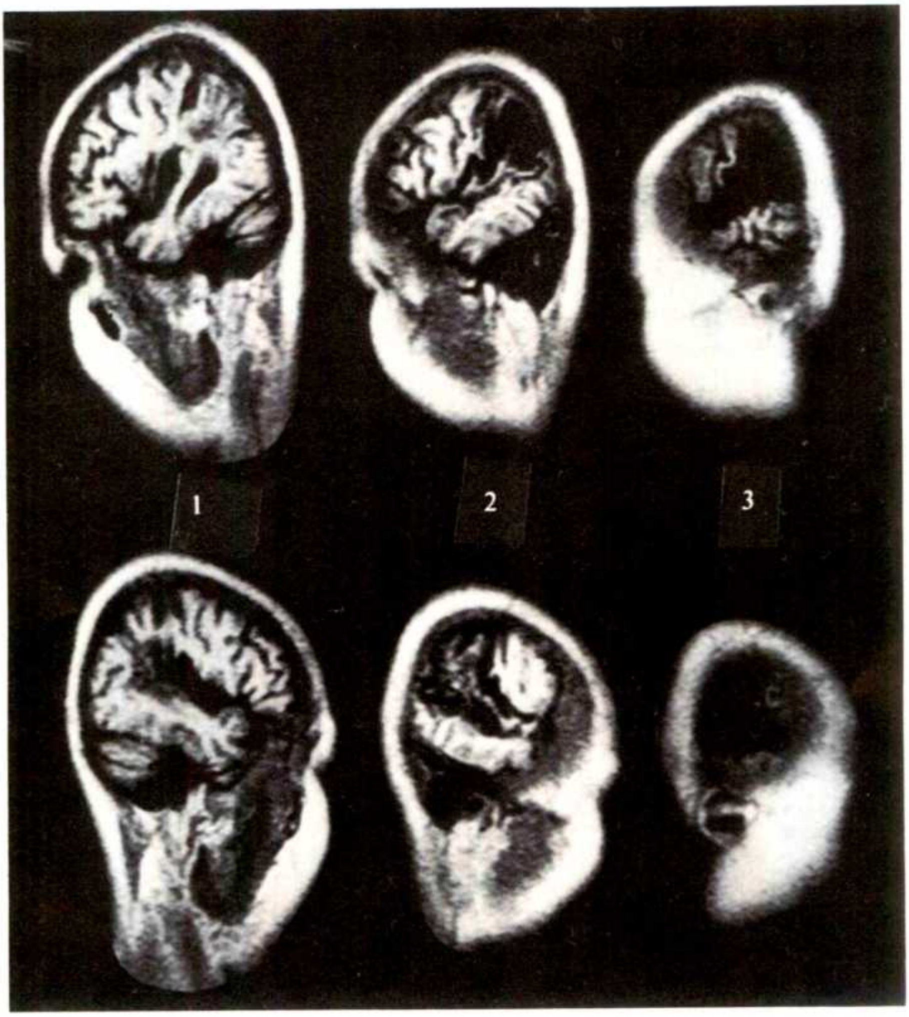


FIG. 4

Audiological Examination (*May 16, 1985*)

The external auditory meatus and ear drums were normal. Impedance audiometry revealed normal tympanic membrane mobility bilaterally. Both ipsilateral and contralateral acoustic reflexes were elicited at normal reflex thresholds. Standard pure tone threshold audiometry showed a mild bilateral sensorineural loss at the lower and higher frequencies. Thresholds for the higher frequencies were more elevated bilaterally, especially on the left (fig. 5). In the range of speech frequencies (500, 1000, 2000 Hz), an average of 15 dB hearing loss was noted in the right ear and 8 dB loss in the left ear. Speech reception threshold could not be determined because the patient was unable to recognize and repeat even a single word. However, she reported that she could hear some sound. The discrimination ability was zero, although the hearing for pure tones was near-normal at the speech frequencies.

TABLE 1. RESULTS OF THE STANDARD LANGUAGE TEST OF APHASIA (SLTA)

Subtest	*Score*
Auditory comprehension	
(words, sentences, commands)	0 correct
Speech	
Naming	100% correct
Explanation of action in a picture	100% correct
Explanation of cartoon	100% correct
Generation of word list	18 animal names/min
Repetition	
(words, sentences)	0 correct
Reading aloud	
(Kanji, Kana, sentences)	100% correct
Reading comprehension	
(Kanji, Kana, sentences, written commands)	100% correct
Writing	
Spontaneous writing	
(Kanji, Kana, explanation of cartoon)	100% correct
Dictation	
(Kanji, Kana, sentences)	0 correct
Calculation	100% correct

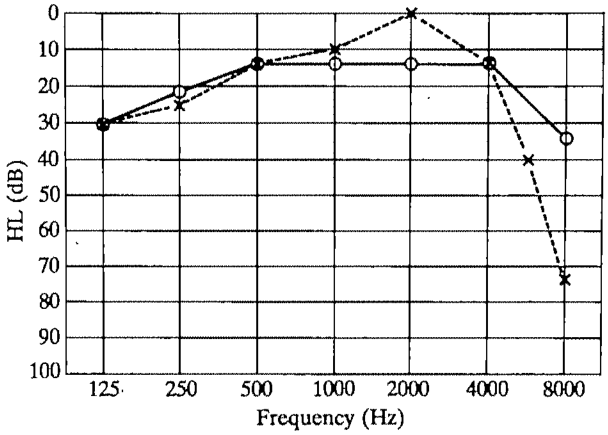


FIG. 5. Pure tone threshold audiometry. × = left ear; o = right ear; HL = hearing level.

Sound localization. The patient was blindfolded and then exposed to a canon sound of about 3 s duration through a tape recorder which was placed at 50 cm from her. The sound was randomly delivered from six directions (right, left, front, behind, above and below). Ten trials were performed in each test. She was correct in 90% of the trials from the right and in 80% of the trials from the left. Accuracy in localizing the sounds from other directions was from zero to 40%. Normals reached 100% correct detection of the sound from all directions. These findings indicate that the patient has a moderate impairment of sound localization.

Nonverbal sound discrimination. The test consists of 25 familiar sounds presented through a tape recorder, including sound-producing objects, animals or events (e.g., a miaowing cat, an ambulance siren). She correctly named 19 sounds.

Distinguishing categories of sounds. The patient was told that she would hear through a tape recorder a sound of one of the following three categories; music (vocal or instrumental), noise and language (English, French, German, Chinese or Japanese), and was asked to categorize the sound. She performed this categorization task almost perfectly; however, she had some difficulty in identifying the gender of a recorded voice and types of musical instruments. Also, she was totally unable to discriminate the languages.

Linguistic Studies

These and the following other special investigations were performed over an eight-week period after admission. All the linguistic tasks were enunciated by the same native Japanese male according to the method of Auerbach *et al.* (1982).

Vowel identification. The patient was asked to identify long vowels (about 1 s duration), a, e, i, o, u; 150 randomly-ordered vowels were presented verbally. Special care was taken to avoid cues from lip-reading or facial gestures. Her average correct response was 47%.

Stop consonant-vowel discrimination. All items were a combination of a consonant and a vowel /a/. The initial stop consonants differed according to a place of articulation (labial /b, p/, alveolar /d, t/, or velar /g, k/) or voicing (voiced /b, d, g/, voiceless / p, t, k/).

1. Binary decision with single distinctive feature. The patient was asked to point out one of two possible choices given in written form in each test. Nine tests of 100 items each were presented. The results are given in Table 2. The average correct response across all the nine tests was 49%.

2. Binary decision with two distinctive features. These tests of 100 items each

TABLE 2. RESULTS FOR STOP CONSONANT-VOWEL DISCRIMINATION: BINARY DECISION WITH SINGLE DISTINCTIVE FEATURES

		Condition		*Nature of distinction*
Distinction	/ba/–/pa/	/da/–/ta/	/ga–/ka/	Voiced/voiceless
% correct	52	50	50	
Distinction	/ka/–/ta/	/pa/–/ta/	/pa/–/ka/	Place of articulation for voiceless stops
% correct	47	52	54	
Distinction	/da/–/ga/	/da/–/ba/	/ba/–/ga/	Place of articulation for voiced stops
% correct	45	47	44	

were presented in the same way as the tests above. The only difference was that the forced choice was between two phonemes that differed by two features instead of one. The following results were obtained: /ka/-/da/ distinction, 50% correct; /ga/-/pa/ distinction 49% correct; /ba/-/ta/ distinction 53% correct. The average correct response across all the 3 tests was 51%.

These linguistic studies indicate that she was able to identify long vowels at a better than chance level but failed in stop consonant-vowel discrimination, with no particular pattern of error, even if the number of distinguishing features increased. From these observations, the patient's 'pure word deafness' seems largely or entirely to be caused by a phonetic decoding defect.

Tests of Musical Capacity

Expressive musical ability. The patient was asked to sing familiar nursery rhymes with the help of written lyrics. Both pitches and rhythms were severely impaired.

Instrumental musical ability. The patient was able to play familiar nursery rhymes on an electric organ with the help of music, but often hesitated during the performance.

Receptive musical ability. 1. *Recognition of melodies.* Free field presentation of 18 nursery rhymes played on an electric organ yielded the following results: verbal identification, 28% correct; a five-way multiple-choice of corresponding pictures, 89% correct.

These results suggest that recognition of melodies was relatively preserved. The poor verbal identification would reflect a defect in retrieving the verbal components.

2. *Tonal pattern discrimination.* The patient was asked to determine whether a sequence of either two or four tones played on an electric organ was ascending or descending. The duration of each tone was about 1 s; 50 items each were administered. The results are shown in Table 3. The patient thus displayed a profound impairment of perception of tonal pattern. In a sequence of four tones, only one octave interval was identified correctly above chance level.

Her failure to distinguish tonal pattern agrees well with the results of experiments

TABLE 3 RESULTS FOR TONAL PATTERN DISCRIMINATION

Two tones		*Four tones*	
Interval*	% correct	Interval*	% correct
1/2 tone	50	1/2 tone	48
Whole	54	Whole	40
Third	34	Third	56
Fifth	52	Octave	76
Sixth	48		
Octave	46		

* Interval between neighbouring tones.

by Diamond and Neff (1957) and Neff *et al.* (1975) who showed that bilateral ablation of auditory cortex in the cat or monkey destroys auditory pattern discrimination.

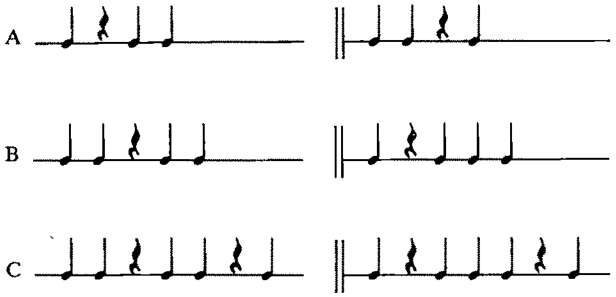


FIG. 6. Examples of pairs of rhythm patterns. A, B and C show pairs of 3, 4 and 5 beats, respectively.

3. *Rhythm discrimination.* Following the method of Mavlov (1980), rhythm perception was investigated using three modalities: auditory (electric organ), visual (penlight flashes) and tactile (taps on the patient's palm). Simple rhythm patterns consisting of 2 to 5 stimuli variously interspaced by 1 or 2 empty stimuli were used (fig. 6). Fifty pairs were presented, and the patient was asked to determine whether two rhythm patterns were the same or different. In all three modalities, they were presented at a 'fast' (200 ms interval) or a 'slow' (1000 ms interval) rate in a random fashion.

Disturbances were seen across all the three modalities at the fast rate but, at the slow rate, the response improved significantly in all modalities; by audition from 52 to 88% correct, by vision from 62 to 94% and by touch from 62 to 88%.

4. *Rhythm reproduction.* For rhythm reproduction, 10 simple rhythm patterns composed of 2 to 5 elements were presented through three modalities in the same way as the previous test. The patient was asked to reproduce the rhythm orally. Each of the above patterns was presented three times for each modality.

Similar results to the previous test were obtained; by audition from 33 to 83% correct, by vision from 57 to 90% and by touch from 40 to 87%.

Neurophysiological Investigation

An MEB-5100 (Nihon Koden, Tokyo) was used in recording auditory evoked potentials (brainstem and late latency auditory evoked potentials). These investigations were performed on May 19, 1985.

Brainstem auditory evoked potentials (*BAEPs*). Clicks (0.1 ms) of 90 dB Hearing Level (HL) were presented at 10 Hz monoaurally. Recordings were derived from Cz to the ear lobe of the stimulated side. The contralateral ear was masked for all trials. Each trial represented 2048 responses. Responses obtained in each ear are presented in fig. 7. All BAEP components (waves I–VI) were recorded with normal amplitude and latency, indicating integrity of the cochlear mechanism and brainstem auditory pathways.

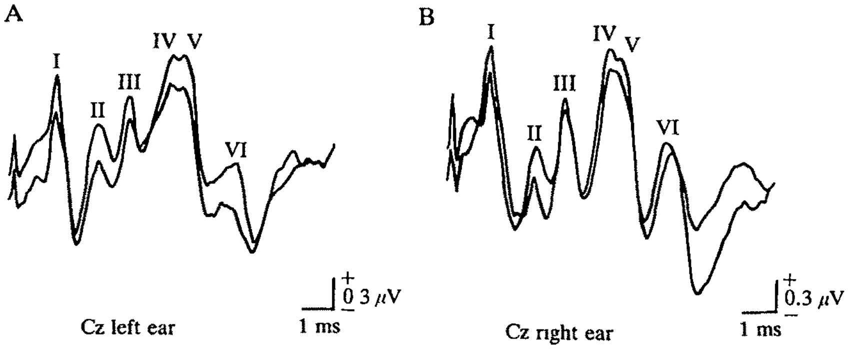


FIG. 7. Brainstem auditory evoked potentials. Recordings are from Cz to the left (A) and to the right (B) ear, respectively; 2048 signals are averaged. Waves I–VI are intact in both tracings.

Late latency auditory evoked potentials (LLAEPs). The click was given to both ears randomly one per 2 s, 100 dB HL. Recordings were derived from Nz to T3 and T4. The low filters were set at 0.5 Hz, and the high filters at 30 Hz. Each trial represented 128 responses in random order. P1, N1, P2 and N2 were easily identified with latencies at about 55, 140, 185 and 225 ms, respectively. The peak latencies were all within normal limits except for N1, which was slightly prolonged. Also, overall late components showed low amplitudes (fig. 8).

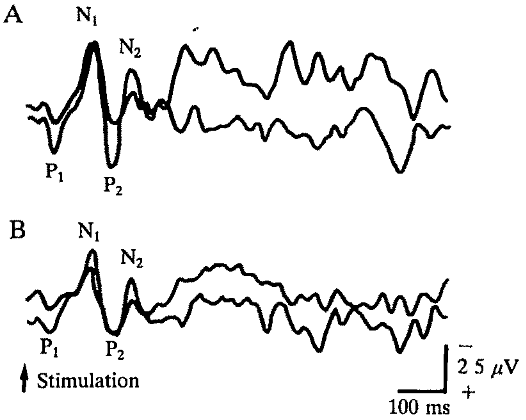


FIG. 8. Late latency auditory evoked potentials. Recordings are from Nz to T3 (A) and to T4 (B), respectively; 128 signals are averaged randomly. Filters are set at 0.5 Hz and 30 Hz.

Neuroacoustic Studies

Threshold-duration function. The patient was asked to tell only whether she heard a sound or not as the duration of the sound was varied over the range from 5 to 1000 ms. Tone bursts generated by an electric stimulator (SEN-7103, Nihon Koden, Tokyo) coupled with an acoustic stimulator (SSS-3100, Nihon Koden) were delivered monoaurally. Fig. 9 shows the relationship between duration and intensity of the

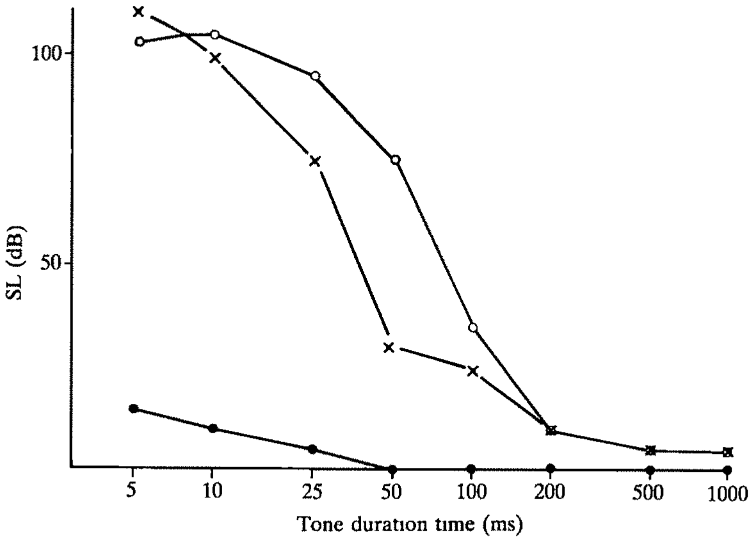


FIG. 9. Threshold-duration at 1000 Hz. Note that the sound intensity decreases as the duration of sounds increases. SL = sensation level. o = patient (L ear); × = patient (R ear); ● = normal subject (both ears).

stimuli to obtain threshold response for both right and left ears at 1000 Hz. As the duration became short, sound intensity had to be raised considerably (100–105 dB Sensation Level, SL) to maintain the threshold response in our patient. In normal subjects the effect was less than 15 dB SL.

Loudness discrimination. Loudness discrimination was tested by the quantal psychophysical method (Jerger *et al.*, 1969). Short-intensity increments were added to a steady-state, pure-tone signal at 5 s intervals. The patient was instructed to indicate verbally whenever she detected a change in the loudness of the steady tone. HL of the steady-state signal was based at 80 dB for 1000 Hz. The patient reached 70% correct detection in the right ear and 50% in the left ear for intensity increment of 3 dB. A 100% correct detection was not achieved until the increment size was 6 dB in both ears. Normal subjects in our laboratory reached 100% correct detection in each ear for an intensity increment of only 2 dB.

Temporal auditory acuity. To examine the temporal resolution of the auditory system, clicks of 0.1 ms duration generated by an MEB-5100 coupled with an SEN-7103 electric stimulator were delivered binaurally through earphones at 100 dB HL. Two tests of click fusion and click counting were performed following the method of Albert and Bear (1974).

1. *Click fusion test.* The interval between two brief binaural pulses was varied, the patient being asked to report whether she heard one or two clicks. Normals can distinguish two clicks at 1 to 3 ms separations (Hirsch, 1975). Our patient, by the method of ascending and descending limits, fused at intervals of 300 ms.
2. *Click counting test.* The patient was asked to count the number of clicks given

in 1 s. The counting in normals ranges from 9 to 11 clicks/s (Auerbach *et al.*, 1982). Our patient was inaccurate for rates greater than 2/s.

The results of both click fusion and click counting tests suggest that our patient had a severe defect in temporal auditory resolution.

3. *Other studies using click sounds.* The perceptual disorder of click sounds was further explored by two methods: (a) threshold-number of clicks and (b) threshold-interval of clicks.

(a) Threshold-number of clicks. The patient was asked to tell only whether she heard clicks or not as the number of clicks was varied over a range from 1 to 128. The interval between clicks was fixed at 10 ms. Threshold was estimated by the method of ascending and descending limits.

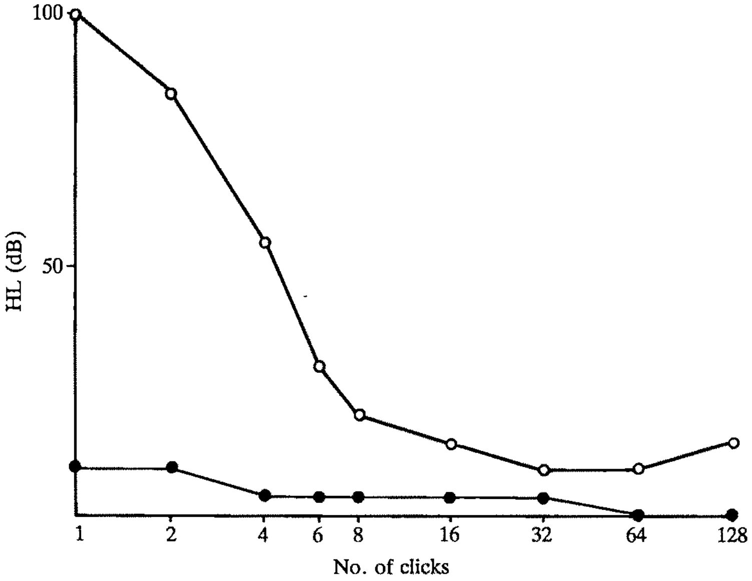


FIG. 10. Threshold-number of clicks. Interval of clicks was fixed at 10 ms. Note that the sound intensity decreases as the number of clicks increases. HL = hearing level. o = patient; ● = normal subject.

Our patient could detect a single click only at 100 dB HL. However, when the number of clicks was increased, the threshold decreased progressively. In normal subjects in our laboratory, the effect was less than 10 dB HL (fig. 10). This phenomenon seems to be due to the effect of temporal summation, which occurs at a cellular level when two or more subthreshold stimuli are applied in close succession (Brinley, 1980).

(b) Threshold-interval of clicks. The threshold with varying intervals of clicks was first examined. The patient was asked to tell only whether she heard clicks or not as the interval of clicks was varied over a range from 1 to 500 ms. The number of clicks was fixed at 2, 4 and 8, respectively. Threshold was estimated in the same way

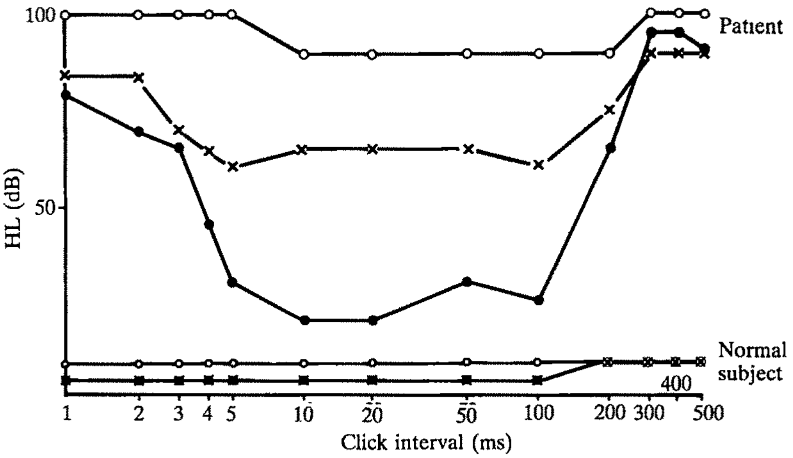


FIG. 11. Threshold with varying intervals of clicks. The number of clicks was fixed at 2, 4 and 8, respectively. As the interval between clicks became shorter from 300 to 100 ms, the threshold decreased but increased again when the intervals of clicks were less than 5 ms. HL = hearing level. o = 2 clicks; × = 4 clicks; ● = 8 clicks.

as the preceding test. As the intervals between clicks were shortened from 300 to 100 ms, the threshold decreased. It remained constant with intervals between 100 and 10 ms and then increased again as the interval shortened. In normals in our laboratory, the effect was less than 10 dB HL (fig. 11).

These results can possibly be interpreted as follows. The lower threshold at click intervals between 300 and 10 ms appears to be due to the effect of temporal summation and the higher threshold at intervals of less than 5 ms may be related to the influence of the relative refractory period. During the initial period of an action potential, the membrane cannot respond to any stimuli, regardless of their intensity; this interval, the absolute refractory period, is approximately 0.4 to 1 ms in mammalian nerve fibres. Following the absolute refractory period, the membrane becomes responsive to stimuli of greater intensity than the normal threshold, that is, the threshold for excitation has been increased. The threshold then declines towards the normal level, this interval representing the relative refractory period (about 3 to 4 ms in mammalian nerve fibres) (Mashima, 1975; Brinley, 1980). From these considerations, the higher threshold at intervals of less than 5 ms can be attributed to the influence of the relative refractory period. However, even within these periods, as the click number was increased, the threshold decreased in our patient, suggesting that temporal summation is also operative during these periods.

To elucidate the relationship between the threshold and the number and interval of the clicks, we administered a further test, the assessment of threshold with varying intervals of clicks within the fixed duration of click burst. The duration of click burst was fixed at 200 ms and within that interval, the number of clicks was increased from 2 to 201, that is, interval of clicks was shortened from 200 to 1 ms. Other methods were exactly the same as the immediately preceding test. At an interval of 200 ms,

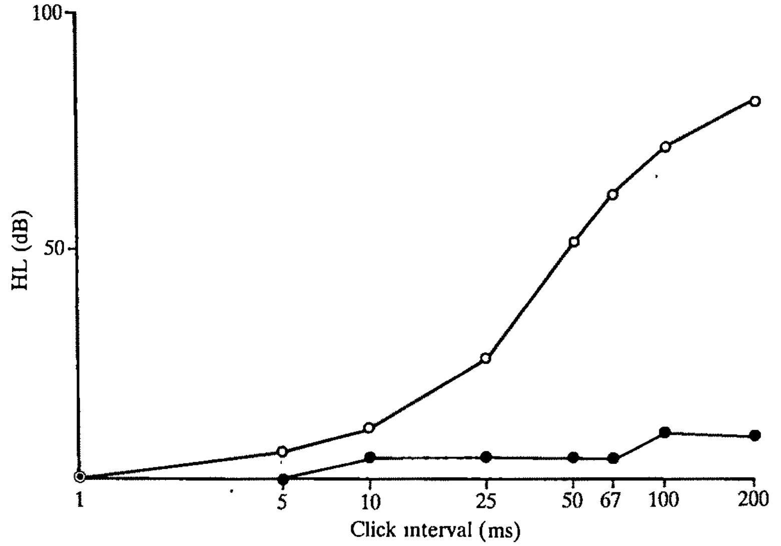


FIG. 12. Threshold with varying intervals of clicks within 200 ms intervals. Duration of click burst was fixed at 200 ms. Note that the threshold decreases as the intervals of clicks are made shorter. HL = hearing level. ○ = patient; ● = normal subject.

our patient could detect a sound only at 80 dB HL. As the interval between clicks was made shorter, however, the threshold for the detection of the sounds decreased progressively. The results at fast click rates agreed nicely with those of fig. 9 for a 200 ms tone burst. In normals, a similar trend was noted with a threshold of less than 10 dB HL throughout (fig. 12). This result confirms that the effect of temporal summation is present in this patient.

Discrimination Test in Various Sensory Modalities

The fact that rhythm perception in this patient improved at a slow rate in all modalities led us to further examination of the relationship between the duration and the interval of various sensory modalities. We designed the following tests for this purpose.

Auditory system. The SEN-7103 electric stimulator coupled with the SSS-3100 acoustic stimulator was used in the following examination.

1. *Duration discrimination test of tones.* A small increment in duration was added successively to a steady-state tone signal at periodic intervals monoaurally. The subject was instructed to indicate verbally whenever she detected a change in the duration of the steady tone. The duration of the steady-state signal was 200 ms, and SL was based at 80 dB for 1000 Hz. In the present case, a duration increment of 380 ms was required to reach 100% correct detection in both ears. Normal subjects in our laboratory reached 100% correct detection by each ear with a duration increment of 20 to 30 ms.

2. *Tone fusion test.* Two tones with the same duration and intensity were presented monoaurally, and the patient was asked to report whether she heard one or two tones as the interval between the two tones was varied. The duration of a tone was varied over the range from 20 to 500 ms. For each duration SL was set at 20 dB above the threshold which had been measured in the threshold-duration function test (fig. 8) except for the 20 ms duration, where SL was 100 dB. Normals in our laboratory could distinguish two tones with an interval greater than 1.0 ms in both ears through all durations. In our patient, the interval necessary to discriminate two tones decreased as the duration of a tone increased (fig. 13).

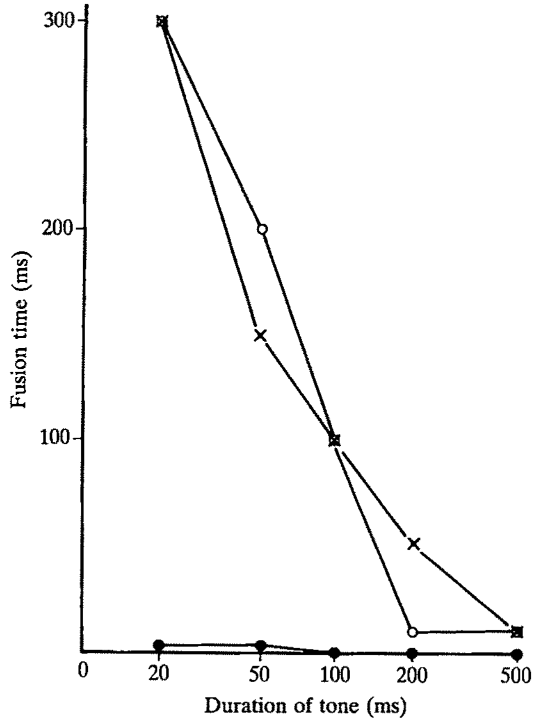


FIG. 13. Tone fusion test. Two tones of the same duration and intensity were presented. Sensation level was 20 dB above the threshold of the duration. Ability to discriminate two tones improved as the duration of a tone was prolonged. o = patient (L ear); × = patient (R ear); ● = normal subject (both ears).

Visual system. 1. *Duration discrimination test of lights.* The ability to detect a small change in light duration was measured with tachistoscopic presentation. Two lights, each being a quadrilateral figure of 15 × 10 cm with a green filter, were projected to the centre of a screen placed in front of the patient at an eye level of 120 cm. Two lights were presented in the same way as the duration discrimination test of tones. The duration of the steady-state signal was 200 ms. In the present case, a duration increment of 300 ms was required to reach 100% correct detection. Normals in our laboratory reached 100% correct detection for duration increment of 40 ms.

2. *Light fusion test.* Two lights of the same figure as in the test above were

presented with a tachistoscope coupled with a two-pulse generator (electric stimulator SEN-7103). Two lights of the same duration were presented and the patient was asked to report whether she saw one or two lights as the interval between two lights was varied. The duration of a light was varied over the range from 5 to 500 ms. A result quite similar to that of tone fusion test was observed, that is, the interval necessary to discriminate two lights decreased as the duration of a light increased (fig. 14). Normals in our laboratory could distinguish two lights for intervals greater than 30 ms through all durations.

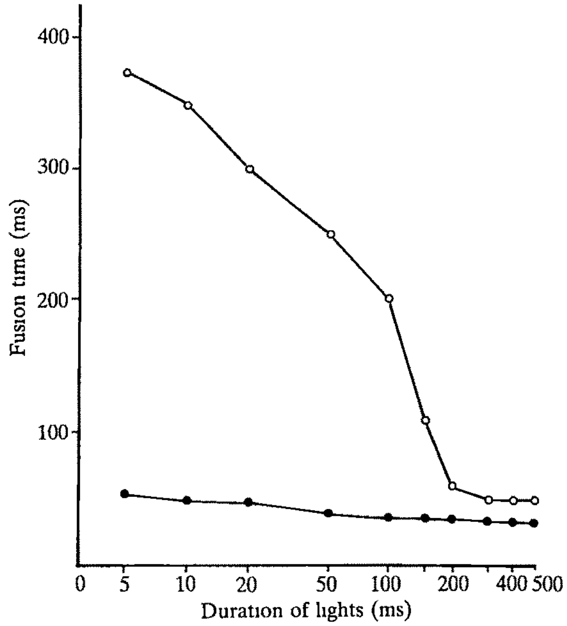


FIG. 14. Light fusion test. Two lights of the same duration were presented. A similar result to that of tone fusion test (fig. 13) was seen. o = patient; ● = normal subject.

Somatosensory system (pain fusion test). Two electric stimulations (0.5 ms, 100 V) were presented in each palm through the general evoked response stimulator SMP-3100 (Nihon Koden, Tokyo) coupled with a two-pulse generator. The interval between two brief pulses was varied and the patient was asked whether she felt one stimulation or two. Normals in our laboratory could distinguish two stimulations with a 20 to 30 ms interval in both palms. This patient fused these stimulations at intervals of 240 ms in the right palm and at 220 ms in the left.

Summary of Major Findings

We have presented a 26-year-old woman with pure word deafness who had cerebral infarcts bilaterally in the temporoparietal lobes. A series of studies revealed the following features. For auditory processing, (1) pure tone threshold audiometry was within normal limits in the frequency range of speech sounds; (2) BAEPs were also within normal limits, and LLAEP components, although low in amplitude, were relatively preserved; (3) sound localization was moderately disturbed; (4) temporal auditory processing as determined by click fusion and click counting was extremely abnormal; (5) ability to discriminate loudness and duration of tones was abnormal; (6) the threshold for detection of a tone decreased as the duration of a tone was prolonged; (7) auditory temporal summation was observed when the number of clicks was increased or the interval of clicks was shortened; (8) ability to discriminate two tones improved as the duration of a tone was prolonged.

For visual processing, (1) ability to discriminate duration of two lights was abnormal; (2) temporal visual processing as determined by light fusion was extremely abnormal; (3) ability to discriminate two lights improved as the duration of light was prolonged. Temporal somatosensory processing as determined by pain fusion was extremely abnormal.

Linguistic studies with natural speech indicated that she had great difficulty in discriminating stop consonant-vowel combinations with no particular pattern of error, but identification of long vowels was better than chance level.

The results of musical ability were as follows: (1) she could sing familiar nursery rhymes, but explosively and monotonously; (2) instrumental musical ability was relatively preserved; (3) ability of melody recognition was also relatively preserved; (4) tonal pattern discrimination was extremely abnormal; (5) disturbance of rhythm perception and reproduction was seen at a fast rate in all modalities, but at a slow rate this supramodal defect improved markedly in all modalities.

Further neuropsychological testing demonstrated some difficulty in discriminating the gender of a recorded voice and types of musical instruments, and great difficulty in discriminating the language of a speaker. Identification of broad categories of sounds was relatively intact and only a mild auditory sound agnosia was demonstrated.

DISCUSSION

The clinical picture in our patient was compatible with pure word deafness. She was unable to comprehend spoken words with intact speech production, reading and writing abilities. Comprehension of nonverbal sounds was also relatively spared. Other features included expressive and receptive amusia. In the following paragraphs, neurophysiological and psychophysical aspects, musical disturbance and the relationship between temporal resolution and auditory comprehension will be discussed.

Neurophysiological and Psychophysical Aspects

Except for only mild hearing loss, our patient had no audiometric defect, and her BAEPs were normal. Hence her poor recognition of linguistic sounds represents a disturbance of central auditory processing. Although low in amplitude, relative preservation of LLAEP components in our patient may be due to residual auditory cortical structures. In the literature which describes cortical auditory evoked potentials in pure word deafness, electrophysiological findings vary from normal to abnormal responses over the left, right or both sides (Albert and Bear, 1974; Shoumaker *et al.*, 1977; Michel *et al.*, 1980; Auerbach *et al.*, 1982). These findings suggest the variability in pathology of patients with pure word deafness.

The moderate impairment of sound localization is consistent with the findings in cats or monkeys after experimental bilateral ablations of the auditory cortex (Neff, 1968; Neff *et al.*, 1975). However, in man this seems to be a variable concomitant (Jerger *et al.*, 1972). As indicated by Jerger *et al.* (1972), this impairment seems to be related to an interaural imbalance in the relation between signal duration and loudness, which was also present in our patient.

In the examination of nonlinguistic auditory stimuli, the present case showed that the threshold for the detection of a sound markedly decreased as the number of clicks was increased or the interval of clicks was shortened. This finding suggests that auditory temporal summation described by Motomura *et al.* (1986) was also present in our case. But their case, unlike ours, had auditory agnosia with bilateral subcortical lesions. Temporal summation appears to exist regardless of symptoms when the bilateral auditory radiations are partially destroyed.

In the present case, a disturbance of temporal resolution was found in all the three sensory modalities tested. This finding has led us to speculate that there is a 'time-organizing system' which is both independent of and central to the sensory mechanism. Efron (1963) found that, compared with right-brain-damaged nonaphasics, aphasics with left hemisphere lesions were severely impaired in determining the order when pairs of tones or coloured lights were presented and that the aphasics with more posteriorly located lesions had more severe visual sequencing difficulties. The subsequent studies of Edwards and Auger (1965), Van Allen *et al.* (1966), Goldman *et al.* (1968), Goodglass *et al.* (1970), Carmon and Nachshon (1971), Albert (1972), Swisher and Hirsh (1972) and Carmon (1978) using sequential auditory and/or visual or audiovisual stimuli, supported this view, although the performance of right-brain-damaged subjects was more impaired than that of normal subjects. Also, in monkeys, the inferior parietal lobule and the banks of the superior temporal sulcus are considered to be a polymodal area (Pandya and Kuypers, 1969; Jones and Powell, 1970; Mesulam *et al.*, 1977; Seltzer and Pandya, 1978, 1980; Bruce *et al.*, 1981; Hyvärinen, 1981). These observations indicate that the 'time-organizing system' might be in the temporoparietal region, predominantly on the left side. However, in the present case, it was only after bilateral temporoparietal lobe infarctions that a marked defect of auditory perception was observed. Hence damage to the temporoparietal regions bilaterally might be necessary for production of marked disturbance of the 'time-organizing system'.

Amusia

In the reported cases of pure word deafness with musical impairment, the disturbance seems to be mainly receptive (Liepmann and Storch, 1902; Bonvicini, 1905; Stertz, 1912; Schuster and Taterka, 1926; Klein, 1927; Reinhold, 1950; Ziegler, 1952; Denes and Semenza, 1975; Auerbach *et al.*, 1982; Coslett *et al.*, 1984). But in our case, musical expression was much more severely involved than musical perception, as in the case of Klein and Harper (1956). Since our patient was unable intelligibly to hear her own words, this may account for her difficulty in musical expression.

This patient had several characteristic disturbances in musical perception. Generally, basic components of music are considered to be composed of the pitch and the rhythm (Wertheim, 1969; Gordon, 1970, 1978; Gates and Bradshaw, 1977). Recognition of pitches was markedly impaired in our case. As for rhythm perception and reproduction, a supramodal defect was seen at a fast rate, supporting the view of Mavlov (1980). However, this condition significantly improved in all modalities at a slow rate, indicating rhythm sense is essentially preserved. Since perception of rhythm requires registration of time intervals, this rate-dependent supramodal defect can be attributed to a supramodal defect in temporal resolution. There is some evidence that rhythm patterns are preferentially processed by the left hemisphere (Halperin *et al.*, 1973; Papçun *et al.*, 1974; Robinson and Solomon, 1974; Gordon, 1978). Also, Mavlov (1980) reported a case of a professional musician who developed a supramodal defect only in the recognition and reproduction of rhythm patterns following a vascular stroke in the left posterior parietal or parietotemporal region. In the light of our own and these findings, we can conclude that rhythm sense probably reflects one aspect of a 'time-organizing system' situated in the temporoparietal region, predominantly in the left.

Thus we believe that the expressive and receptive musical disabilities in this patient are secondary to central hearing loss.

Our patient was able to discriminate broad categories of sounds: voices, music and environmental sounds; however, she was unable to distinguish foreign languages. Also, she had some difficulty in identifying types of musical instruments and the gender of a recorded voice. From these observations, it seems that she had difficulty in distinguishing sounds belonging to the same 'timbre category'. It has been reported that the right hemisphere is responsible for perception of the intonation contours of speech (Blumstein and Cooper, 1974) and for timbre perception (Milner, 1962; Kallman and Corballis, 1975; Mazzucchi *et al.*, 1982). Hence her difficulty may reflect the larger right hemisphere lesion.

With regard to melody recognition, her ability was relatively preserved. Bever and Chiarello (1974) called attention to the possibility that different nervous structures may be engaged in the processing of musical stimuli, depending on the subject's contact with music and that a melody may be perceived either as its overall melodic contour or as an organized arrangement of components. Bever and Chiarello (1974) concluded that naive listeners do in fact perceive melodies in a gestalt fashion and that the processing is predominantly in the right hemisphere, while musically experienced listeners perceive melodies in an analytic fashion and that the processing is predominantly in the left hemisphere. Hence, in the light of her experience in music, her relatively preserved melody recognition in the presence of a large right hemisphere lesion may be due to an interaction of the right and left hemisphere functions.

Relationship between Temporal Resolution and Auditory Comprehension

In the present case, the clinical defect was limited only to auditory modality, although psychophysical data revealed a supramodal defect in the temporal resolution of these modalities. This finding suggests that the auditory modality is much more dependent upon a temporal resolution than other sensory modalities. Somatosensory and visual perception demands more spatially-orientated data processing. Therefore, these capacities of hers would have not been affected. Also, she had an extremely abnormal click fusion and click counting ability. Especially, the threshold of click fusion (300 ms) was much higher than those reported by others: 15 ms in Albert and Bear (1974) and 30 ms in Auerbach *et al.* (1982). These findings support the view of Albert and Bear (1974) who emphasized that the defect in auditory temporal resolution was an important factor for the development of pure word deafness. However, there still remains a problem which cannot be explained by this hypothesis. Her auditory comprehension did not improve at all, even if she was spoken to slowly enough, despite the marked improvement in temporal resolution as the duration of a tone was prolonged. This indicates that there are other factors besides a defect in auditory temporal resolution for the poor recognition of spoken words in this case. This patient had marked impairment in discrimination of loudness, pitch and tone duration. In addition, she often complained that a human voice sounded like an echo. These factors and/or other unknown factors may be responsible for her poor recognition of spoken words.

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RETINAL VENOUS SHEATHING IN OPTIC NEURITIS

ITS SIGNIFICANCE FOR THE PATHOGENESIS OF MULTIPLE SCLEROSIS

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SUMMARY

A systematic study of the frequency of retinal vascular abnormalities and cells in the media has been made in 50 patients presenting with acute optic neuritis. Abnormalities were found in 14 (fluorescein leakage in 10, perivenous sheathing in 6, cells in the vitreous in 6 and in the anterior chamber in 4; in 2 the cells in the media were seen without vascular changes). After a mean follow up of 3.5 years multiple sclerosis (MS) had developed in 8/14 patients with vascular abnormalities and/or evidence of inflammation and in 5/32 without; the difference is significant ($P < 0.02$). The occurrence of perivenular abnormalities in a region free of myelin and oligodendrocytes provides evidence that the vascular changes in MS can occur independently of contiguous demyelination, and may be the primary event in the formation of a new lesion.

INTRODUCTION

It has long been known that the cerebral venules are abnormal in the lesion of multiple sclerosis (MS): the plaques are orientated around them and perivenous cuffing is a prominent feature of the active lesion (Dawson, 1916; Prineas, 1975; Allen, 1981, 1984). Vascular abnormalities have also been detected in the retina in MS by ophthalmoscopy (Rucker, 1944, 1945, 1972; Orbán, 1955; Møller and Hammerberg, 1963; Haarr, 1964; Younge, 1976; Bamford *et al.*, 1978; Engell and Andersen, 1982) but their significance has remained uncertain because of disagreement about the frequency and even the validity of the findings and because little is known about the functional integrity of the apparently abnormal retinal vessels.

Optic neuritis is a common presenting manifestation of MS. We report here the results of a systematic clinical and fluorescein angiographic study of the retinal blood vessels and their integrity in this condition. We found vascular abnormalities

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and/or cells in the media in one-quarter of patients presenting with their first attack of apparently 'isolated' optic neuritis and have assessed the significance of this finding as a risk factor for the subsequent development of MS.

PATIENTS AND METHODS

Consecutive patients presenting to the Physicians' Clinic at Moorfields Eye Hospital with a diagnosis of optic neuritis were assessed. Those with a past history or signs of other ocular disease, neurological symptoms or signs suggestive of MS or other systemic disease which may be associated with ocular abnormalities, were excluded. Fifty patients were investigated. Of these, 31 were female and 19 male. The mean age at presentation was 29.2 years (range 14–49). All fulfilled criteria for the diagnosis of acute unilateral idiopathic optic neuritis: acute onset of blurring of vision, usually associated with pain on eye movement (8 did not have it). Only 1 patient failed to show spontaneous improvement. Three patients had had a single previous episode of optic neuritis 11 years, 4 years and 3 years prior to entering the investigation. The remainder were presenting with their first episode of isolated optic neuritis. In keeping with our usual practice (Gould *et al.*, 1977) no patients were treated.

Following routine neurological and ophthalmological assessment, which included a slit lamp examination, the pupils were dilated and the fundus examined by indirect ophthalmoscopy. Fluorescein angiography was performed on all patients. X-rays of the chest, skull and optic foramina were performed, as were serological tests for syphilis and a full blood count. A pattern reversal visual evoked potential (VEP) examination was carried out on 31 patients.

During the first 3 to 6 months after presentation, the patients were seen at 1 to 4-week intervals, when the ophthalmological and neurological examinations were repeated. Forty-six of the original 50 patients were recently reassessed neurologically and HLA typed. Two patients declined to attend for review, but in discussion on the telephone stated that they had had no further symptoms. Two patients were lost to follow-up. The mean length of follow-up from the first episode of optic neuritis was 3 years and 6 months (range 1 month to 11 years 10 months).

Tissue Typing

HLA-A, -B, -Cw and -DR typing was carried out by conventional microcytotoxicity testing (Terasaki and McClelland, 1964; Bodmer *et al.*, 1978). The typing sera used to define these antigens were obtained locally or donated by typing laboratories. All had either been used in the Histocompatibility Workshops or characterized by testing on cell panels previously tested with Workshop sera. In most instances at least 4 well-defined antisera were used for detection of each HLA specificity and positive typing for any antigen was based on concordant reactions with at least 2 of these. For comparison, a control group of 164 healthy volunteers were tissue-typed for HLA-A, -B, -Cw and -DR antigens. These were unrelated Caucasoids, mostly laboratory workers, originating from the south-east of England. Significance was determined with the χ^2 test with Yates correction for continuity. The relative risk (RR) was calculated according to Svejgaard *et al.* (1975) using the formula:

$$\mathrm{RR} = \frac{\text{No. of patients positive}}{\text{No. of patients negative}} \times \frac{\text{No. of controls negative}}{\text{No. of controls positive}}$$

A value greater than unity signifies an increased risk and a value less than unity, a decreased risk.

Visual Evoked Potentials (VEPs)

The VEP examinations were carried out at the National Hospital, Queen Square, in the laboratory of Dr A. M. Halliday. The pattern reversal technique was used and the details of the methods have been published (Halliday, 1982).

RESULTS

Ophthalmoscopic Findings

Fourteen of the 50 patients showed evidence of retinal vascular abnormality and/or cells in the media (Table). Sheathing of the peripheral retinal venules (fig. 1) was present in 6. In no case were aberrant myelinated nerve fibres seen in the retina and in no case was sheathing present close to the disc; in only 1 was it visible at the posterior pole without pupillary dilatation. Fluorescein angiograms showed peripheral focal leakage of dye (fig. 2) in 4 of the 6 cases with ophthalmoscopically abnormal venules. The segments of abnormal permeability corresponded with the sheathed segments when present, but in 6 additional cases, peripheral focal leakage of fluorescein was seen in the absence of ophthalmoscopically visible vascular abnormality.

In 6 patients there were cells in the vitreous visible with the slit lamp and in 4 of them there were cells in the anterior chamber as well. Four of the patients with

TABLE. RETINAL VASCULAR ABNORMALITIES AND/OR CELLS IN THE MEDIA IN OPTIC NEURITIS

Perivenous sheathing	2
Perivenous sheathing plus fluorescein leakage	4
Fluorescein leakage without sheathing	6
Cells in media only	2
	14
No additional ocular abnormality	36
Total	50

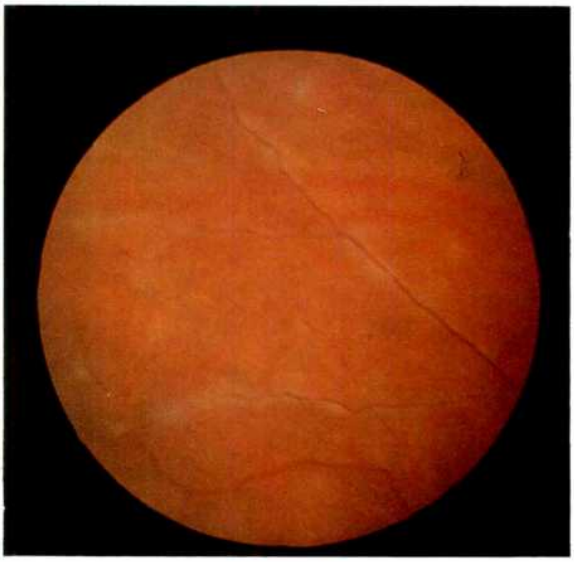

FIG. 1. Peripheral fundus photograph showing perivenous sheathing.

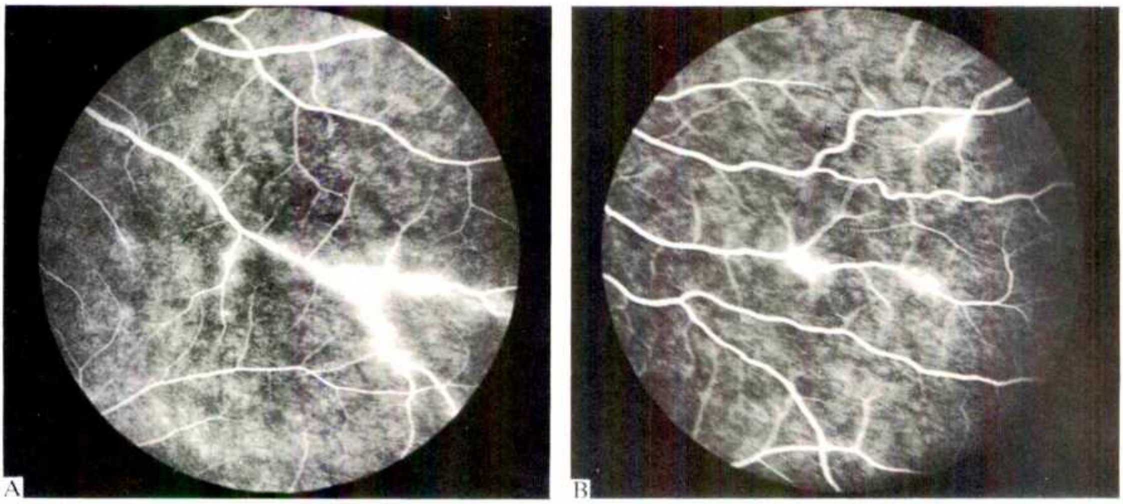

FIG. 2. A, B, Fluorescein angiograms showing multiple sites of leakage in different parts of retinal periphery in the same patient as that of fig. 1.

cells in the media also showed evidence of sheathing and/or fluorescein leakage. In none was the presence of cells in the media suspected without the use of the slit lamp. The sheathing, fluorescein leakage and cells in the media were ipsilateral to the symptomatic eye in 9, contralateral in 4 and bilateral in 1. No patient showed vitreous infiltrates or conjunctival or iris nodules suggestive of sarcoidosis. Two of the patients with cells in the anterior chamber had small keratic precipitates. Chest x-rays and the haematological investigations were normal in all patients.

Clinical ophthalmological reassessment including indirect ophthalmoscopy was carried out for 6 to 24 months after presentation. In no patient did the sheathing disappear. In 49/50 patients the visual acuity returned to 6/9 or better; the one patient who showed no recovery had a final acuity of 6/18.

Development of Multiple Sclerosis

Forty-six of the 50 patients (including all those with vascular abnormalities and/or cells in the media) were reassessed neurologically 1 month to 11 years 10 months (mean 3.5 years) after the first episode of optic neuritis in order to determine the frequency of development of MS. The diagnostic criteria of Poser *et al.* (1983) were used. The overall incidence of clinically definite or clinically probable MS was 13/46 (28%), which is similar to the figure obtained by Compston *et al.* (1978) 3½ years after presentation with optic neuritis. When the two groups of patients (with and without abnormalities of the vessels or media) were considered separately, the frequency of MS was higher in the former (8/14) than in the latter (5/32). The 4 patients who were not reviewed were all in the group without additional ocular abnormalities. The difference is significant ($P < 0.02$). When the 3 patients who had had a previous attack of optic neuritis are excluded (1 from the group with sheathing and leakage who had not developed MS and 2 from the group without additional ocular abnormalities), the frequency of MS was 8/13 in the vascular/inflammatory group and 3/30 in the remainder. The difference is more significant ($P < 0.005$). The relative risk for the development of MS was 14.4. In both groups, females were more likely to have developed MS than males. The interval between the presenting episode of optic neuritis and the next clinically expressed episode of abnormality in the central nervous system (CNS) (within or beyond the visual system) was less in the patients with additional abnormalities (mean 6.5 months; range 1–28 months) than in those without (mean 14 months, range 1–36 months) but the numbers are too small for accurate analysis.

HLA Typing

The 46 patients who were reviewed neurologically were HLA typed (46 for A, B, Cw, and 45 for DR). The results were similar to those reported previously for optic neuritis (Compston *et al.*, 1978; Fielder *et al.*, 1981). The frequency of HLA-DR2 was significantly higher in patients with optic neuritis than in the control population of normal individuals (47% versus 21% in controls, $P < 0.005$, RR = 3.2). The association with HLA-DR2 was still present when the two groups with and without vascular abnormalities or cells in the media were considered separately (50%, $P < 0.05$ and 45%, $P < 0.01$, respectively). The overall increase in risk for the development of MS in the presence of HLA-DR2 was also confirmed (54% versus 21% in healthy controls, $P < 0.05$, RR = 4.3).

Visual Evoked Potentials

Visual evoked potential examinations were carried out in 31 patients, including 10 of the 14 with vascular abnormalities and/or cells in the media. Abnormalities characteristic of those seen in optic neuritis (Halliday *et al.*, 1972; Halliday and McDonald, 1981) were found. Of the 10 patients with additional ocular abnormalities 2 had absent P100s in one eye, 7 had delayed P100s in at least one eye (2 of them in both eyes) and 1 patient had normal latency P100s in each eye. Of the patients in this group, therefore, 90% had abnormal VEPs and 70% delayed VEPs.

Of the 21 patients without additional ocular abnormalities 2 had absent P100s in one eye, 14 had delayed P100s in at least one (one of these in both eyes) and 5 patients had P100s of normal latency from both eyes. The overall percentage of abnormal VEPs in this group was therefore 76% and the overall percentage with delayed VEPs 67%.

The overall percentage of abnormal VEPs was 80.7% (25 out of 31 patients) and the overall percentage of delayed VEPs 67.7% (21 out of 31). There was no significant difference between the mean P100 latency in the two groups, which was 119.56 ± 16.89 ms for those with additional ocular abnormalities and 118.63 ± 18.80 ms for those without.

DISCUSSION

Vascular abnormalities and/or exudation of cells into the media were present in about one-quarter of our patients with acute isolated optic neuritis. Reports of sheathing in MS have made passing reference to its presence in occasional cases of optic neuritis. Younge (1976) examined 37 such patients and found sheathing in only 1. The explanation for the lower frequency is not certain but probably lies in methodological differences. All but 3 of our patients were examined within 8 weeks of onset; the timing of the examination in Younge's study is not stated. The method of examination may also have differed. The pupils were dilated in all our cases and we used the binocular indirect ophthalmoscope, which is more satisfactory for examining the retinal periphery than the direct ophthalmoscope.

Sheathing has been reported in 10 to 20% of patients with MS but not all have found it (*see* review by Rucker, 1972) and most neurologists have been reluctant to accept the observation, having failed to see it for themselves. Few, however, are experienced in the systematic examination of the periphery of the retina and it should be emphasized that in only 1 of our patients were abnormalities visible at the posterior pole through the undilated pupil. That the changes are pathological and not just a light reflex (Field and Foster, 1962) was unequivocally shown by the focal leakage of fluorescein from sheathed portions of the vessels both in the present study and in MS (Younge, 1976; Bamford *et al.*, 1978).

It is important to establish that the patients we studied were representative of acute idiopathic optic neuritis and that none had a specific identifiable cause for visual loss. The age and sex distribution of the patients, the mean age of onset of optic neuritis, the overall incidence of MS after 3.5 years, and the association with HLA-DR2 are in accord with previous reports from the same geographical region (reviewed by McDonald, 1983). The VEP changes were typical of optic neuritis (Halliday *et al.*, 1972; Halliday and McDonald, 1981) although they are not specific; there were no differences between the patients with vascular abnormalities and/or cells in the media and those without. No patient had to be excluded because of radiological or haematological abnormalities and none had evidence of other ocular disease. The persistence of remission in all but 1 case (who later developed MS) makes nerve compression improbable.

The most troublesome source of potential diagnostic confusion in this series of patients is sarcoidosis, a condition in which peripheral retinal phlebitis with cells in the media is common. Optic nerve involvement in sarcoidosis is often accompanied by prominent swelling of the nerve head due to infiltration: marked swelling was not seen in any of our patients. None had other evidence of ocular sarcoidosis. Lasting spontaneous remission of an acute optic neuropathy (as experienced by all our cases with retinal vascular abnormalities) is rare in sarcoidosis, although steroid-induced temporary remission is less so (Graham *et al.*, 1986). All the patients in the present investigation were fit and chest x-ray and blood counts were normal. None had a history of erythema nodosum. While we cannot exclude the possibility that some had sarcoidosis, there is no evidence that they did.

Clinical Implications

In the present study it was not possible to determine whether the retinal vascular abnormalities or cells in the media appeared at the time of the attack of optic neuritis or earlier. The significantly higher frequency of MS in the group of patients with sheathing and/or evidence of inflammation after a comparatively short period of follow-up suggests that from the clinical point of view its presence is of predictive value in assessing the risk of development of clinically expressed MS or the rate at which it does so, and in that respect is equivalent to finding evidence (clinical or on investigation) of lesions in central white matter outside the optic nerve. This interpretation is consistent with the observation that in 5 patients the abnormalities were bilateral or contralateral.

Pathogenetic Significance

It is noteworthy that there are similarities between the vessels and perivascular tissue in the white matter of the CNS, including the optic nerve and the retina. In both retina and brain there are continuous endothelial tight junctions (Hogan *et al.*, 1971; Goldstein and Betz, 1983). Processes from astrocytes in the CNS and the Müller cells in the retina ensheath the vessels, being separated from the endothelium by basement membrane and pericytes. The walls of the larger vessels contain collagen fibrils and muscle cells. At both sites there is selective permeability to a variety of molecules (Cunha-Vaz *et al.*, 1966; Bradbury, 1979). Both astrocytes and Müller cells can express glial fibrillary acidic protein (Bignami and Dahl, 1979). In MS perivascular cuffing is commonly observed in histological sections of the brain and can be seen readily in the retina (Arnold *et al.*, 1984; I. V. Allen, unpublished observations), where it has been observed to correspond with segments of ophthalmoscopically observed sheathing (Fog, 1965; Klintworth, 1982). We therefore suggest that the sheathing of retinal vessels that we observed ophthalmoscopically is the visible clinical sign of the perivascular lymphocytic infiltration and accompanying oedema which characterizes the lesions of MS.

Class II HLA molecules have a critical role in the pathogenesis of autoimmune diseases (Bottazzo *et al.*, 1983). The induction of Class II MHC molecules occurs in tissues involved in cellular immune responses, for example in organ allografts undergoing rejection (Hall *et al.*, 1984), tissues damaged by graft-versus-host disease (Suitters and Lampert, 1984) and cerebral venules in the T cell-mediated experimental disease, experimental allergic encephalomyelitis (Wekerle, 1984). It would be of considerable interest to know whether similar changes occur in the human retinal vessels of patients with sheathing.

The perivascular cuffing in the retina in optic neuritis and MS occurs in a region which is free of myelin and oligodendrocytes (Hogan *et al.*, 1971) which cannot therefore be necessary for the initiation of the cellular infiltration. Such a conclusion argues strongly against the view that the vascular changes in MS are secondary to myelin breakdown produced in some other way (*see* discussion by Allen, 1981, 1984) and focuses attention on the possibility that the primary events leading to demyelination occur at the vascular endothelium. Adams *et al.* (1985) have also argued for such a view on the basis of their observations on inflammatory vasculitis in the brain in MS. Why the peripheral venules of the retina are particularly liable to damage is uncertain, but might be related to the relative slowness of blood flow at this site. This might facilitate deposition of viruses during a phase of viraemia, and allow patrolling T cells maximum opportunity for interaction with the endothelial surface.

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ORIENTATION-SELECTIVE VISUAL LOSS IN PATIENTS WITH PARKINSON'S DISEASE

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SUMMARY

Visual contrast sensitivity was measured using 2 cycle/deg sinewave gratings of different orientations in 10 patients with Parkinson's disease and in 15 age-matched controls. Loss of visual contrast sensitivity was found in 6 patients, all of whom had normal visual acuity. Visual loss depended on grating orientation; in all cases the maximum sensitivity loss was for the horizontal. Sensitivity loss was most marked at a temporal frequency of 4 to 8 Hz. Visual fields gave no hint of the orientation selectivity. We conclude that orientation selectivity implicates visual cortical cells in Parkinson's disease. We tentatively suggest that a preferential loss of contrast sensitivity to horizontal gratings might be due to a functional abnormality in the striate cortex that relatively spares the extrastriate cortex. The dependence of visual loss on temporal frequency combined with the sparing of visual acuity might possibly be understood if Parkinson's disease preferentially affects the visual pathway leading from the retina to cortex via the magnocellular layer of the lateral geniculate nucleus. There is an intriguing similarity between the pattern of visual loss in Parkinson's disease and in multiple sclerosis.

INTRODUCTION

Parkinson's disease is classically associated with motor signs such as tremor, bradykinesia, rigidity and abnormalities of gait and posture; visual sensory abnormalities were not thought to be included. In recent years, however, it has been found that the visual system is also involved: abnormalities of visual evoked potentials have been detected in patients with Parkinson's disease (Bodis-Wollner and Yahr, 1978; Gawel *et al.*, 1981; Kupersmith *et al.*, 1982; Regan and Neima, 1984*a*; Tartaglione *et al.*, 1984), and it has subsequently been shown that some parkinsonian patients experience sensory visual loss (Bodis-Wollner *et al.*, 1984; Regan and Neima, 1984*b*).

At this time, the pathophysiology of the sensory visual loss in parkinsonian patients is unknown. The aim of the present study was to provide clues to the mechanism of visual sensory damage in Parkinson's disease. We measured visual contrast sensitivity by means of sinewave grating test targets. It is accepted that sinewave gratings can detect visual loss hidden to the Snellen acuity test, and they have been widely used to study visual dysfunction in neuro-ophthalmological disorders; their clinical use has been succinctly reviewed by Wolkstein *et al.* (1980). In

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brief we found that in 6/10 patients, visual contrast sensitivity to a horizontal grating was abnormally less than visual sensitivity to a vertical grating. We infer that cortical neurons are involved because orientation-sensitive neurons are not found peripheral to the primary cortex. Because cortical area V2 in the primate is biased for vertically orientated stimuli while area V1 has roughly equal biases for horizontal and vertical, we tentatively suggest that these 6 patients may have experienced functional loss in the human equivalent of V1 that relatively spared V2. Orientational selectivity in parkinsonian patients was greatest when the test grating was modulated at a temporal frequency of 4 to 8 Hz. Cells in the retina-lateral geniculate nucleus (LGN) magnocellular layer-cortical pathway of the primate respond best to low spatial frequency gratings in this temporal frequency range; if Parkinson's disease can preferentially affect cells in this pathway, a sensitivity loss to a 2 cycles/deg, 8 Hz grating that spares visual acuity might be understood.

METHODS

Grating Contrast Sensitivity Measurements

Sinewave gratings were generated on a CRT (Tektronix model 608 with green, type 31 phosphor) by a 'Picasso' image generator (Innisfree Electronics). The grating was of spatial frequency 2 c/deg, and was counterphase-modulated by a sinewave. Except where stated otherwise, the modulation rate was 8 Hz. The CRT screen was circular, subtended 3.5 deg diameter, had a mean luminance of 18 $cd \cdot m^{-2}$ and was surrounded by a uniformly-illuminated green field of approximately the same luminance subtending 30 × 30 deg. Grating contrast was calibrated with a radiometer (Tektronix model J6523).

Subjects varied grating contrast by turning a knob. Before recording any measurements, subjects went through a training session. Starting from zero contrast (i.e., a blank screen of luminance 18 $cd \cdot m^{-2}$), they were instructed to turn the knob so that the CRT screen looked just different from a blank screen. They were then asked to describe the appearance of the screen. All subjects described the screen in terms of moving or flickering light and dark blotchy areas. This we called *flicker threshold.* Then subjects were instructed to set the knob so that they could just see bars that extended right across the screen. This we called *pattern threshold.* Before recording any measurements, each subject made a series of practice settings of these two thresholds. Thresholds were taken as the mean of 10 settings. Sensitivity was defined as the reciprocal of threshold. In any given session, pattern and flicker thresholds were measured for vertical (0 deg), horizontal (90 deg), and the two oblique grating orientations presented in random order. The orientational tuning ratio was defined as (S_1/S_2) where S_1 was the highest contrast sensitivity and S_2 was the lowest contrast sensitivity of the four orientations. Contrast sensitivity is the reciprocal of contrast threshold (T%), so that a sensitivity of 100 means that T was 1.0%, and so on.

Visual Fields

Bjerrum screen fields (Scott, 1957) were measured at a viewing distance of 1 m. The black cloth had a luminance 0.26 $cd \cdot m^{-2}$ and the white targets were of luminance 11.3 $cd \cdot m^{-2}$, so that incremental contrast was 44. (Incremental contrast was defined as $(L_1\text{-}L_2)/L_2$ where L_1 was the luminance of the spot and L_2 the luminance of the surround.) Visual fields were also assessed using the 'Octopus' automatic perimeter. Lastly, we measured kinetic visual fields using a blurred spot of diameter 0.25 deg projected onto a white screen of luminance 200 $cd \cdot m^{-2}$. (Spot diameter was chosen to approximate the width of a bright bar in a 2 c/deg sinewave grating.) The spot's incremental contrast was set at

28%, 18% or 9%. Subjects wore the appropriate corrective lenses for the viewing distance of 434 cm (171 inches).

Letter Charts

High-contrast (84%), intermediate-contrast (25%) and low-contrast (7%) letter charts were projected onto a screen and viewed from 20 ft. The luminance of the white parts of the screen was 100 cd·m^{-2}. The charts are illustrated in Regan and Neima (1984*a*). The equivalent Snellen acuities for the high-contrast chart were as follows: line 5, 20/40; line 6, 20/30; line 7, 20/25; line 8, 20/20; line 9, 20/15; line 10, 20/13; line 11, 20/10. Letter reading scores were calculated as follows. Each line comprised 8 letters. Suppose that a patient read all lines correctly up to line 8, but read only three letters correctly on line 9; the patient's score was expressed as $8\frac{3}{8}$, i.e., 8.375 rounded off to 8.4. Normal limits were defined as the control mean ± 2.5 SD.

Control Experiment: Visual Field Restriction

Flicker and pattern contrast sensitivities for horizontal and vertical gratings were measured for 3 control subjects using the full 3.5 deg diameter field. Visual field loss was then mimicked by placing an aperture in front of the circular grating stimulus, so that only a 3.5 deg × 1.5 deg horizontal slit-shaped area of grating was visible, and the measurements were repeated. Finally, the slit was narrowed to 3.5 × 1.0 deg, and the measurements repeated.

Results were calculated as follows. The ratio $(T_H/T_V)_{FF}$ between horizontal and vertical thresholds was obtained both for the full-field stimulus and also for the 1.5 deg aperture $[(T_H/T_V)_{1.5}]$ and 1.0 deg aperture $[(T_H/T_V)_{1.0}]$. Ratios were separately calculated for flicker and for pattern. The effect of restricting the field to a 1.0 deg slit was calculated as $[(T_H/T_V)_{1.0} - (T_H/T_V)_{FF}]$ and expressed as a percentage. Corresponding calculations were made for the 1.5 deg slit.

Patients and Control Subjects

The patient group comprised 4 males and 6 females, all of whom were receiving medication for Parkinson's disease at the time of the study. At the time of testing, the medication exerted optimal control on the disease. Table 1 gives clinical summaries and medication at the time of testing, i.e., November 1984–May 1985. Ages ranged from 52 to 71 yrs (mean 62.5 yrs). The control group comprised 3 males and 12 females, none of whom had any history of neurological or ophthalmological disorder. Ages ranged from 43 to 75 yrs (mean 60.5 yrs). All patients and control subjects gave informed consent after the aims and nature of the study had been explained. All patients were informed that they were free to leave the study at any time without any prejudice as to their continuing medical care.

RESULTS

Pattern and Flicker Thresholds in Control Subjects

Considering each individual subject's most insensitive orientation only, and using a 2 c/deg, 8 Hz grating, mean contrast threshold was 1.32% for flicker, SD 0.17%, giving an upper normal limit of 1.75%. Corresponding figures for pattern threshold were 1.33%, SD 0.27%, giving an upper normal limit of 2.0%. (The 99% control limits were calculated as the mean +2.5 SDs for the control group.) Orientation tuning ratios were calculated for each individual control subject, and upper normal limits taken as the control mean +2.5 SDs of the control group. The control population showed no significant bias for any orientation. Contrast sensitivities rather than thresholds were plotted in figs 1–4.

TABLE 1. CLINICAL SUMMARIES

Case	*Sex*	*Age (yrs)*	*Medication** *L*	*B*	*A*	*Clinical history*
1	M	61	400			Symptoms began 1977; tremor of hands R > L; rigidity; mild bradykinesia
2	F	65	300			Symptoms began 1982; tremor of hands L > R; cogwheel rigidity of arms L > R; mild difficulty with postural reflexes
3	F	71	1250			Diagnosed 1982 (unclear when symptoms began); mild bilateral limb tremor; difficulty with postural reflexes
4	F	66	500			Diagnosed 1983; cogwheel rigidity; bradykinesia; minimal tremor; significant problems with loss of postural reflexes
5	F	56		10		Symptoms since 1984; mild bilateral limb tremor; bradykinesia; mild problems with postural reflexes
6	M	69		15		Symptoms since 1984; bradykinesia; rigidity; mild bilateral limb tremor
7	F	71	250			Symptoms since 1983; limb tremor of moderate severity R > L; bradykinesia; mild difficulties with postural reflexes
8	M	60	375	10	200	Symptoms began 1980; marked bradykinesia, cogwheel rigidity; minimal tremor; moderate problems with postural reflexes
9	F	54	750	15	400	Symptomatic since 1975; marked tremor of limbs R ≫ L; bradykinesia, rigidity; minimal difficulties with postural reflexes; peak-dose dyskinesia; 'on-off' episodes rarely
10	M	52	625	17.5		Symptomatic since 1979; marked bradykinesia, rigidity; minimal tremor; 'on-off' episodes occasionally

* L-DOPA (L), bromocriptine (B), and amantidine (A) are shown in mg/day. L-DOPA was taken in combination with carbidopa (Sinemet).

Parkinsonian Patients: Absolute Sensitivities for Pattern and Flicker

Of 20 eyes tested with horizontally-orientated 2 cycles/deg, 8 Hz gratings, 7 were abnormally insensitive to pattern (6/10 patients), 5 were abnormally insensitive to flicker (5/10 patients) and 5 were abnormally insensitive to both pattern and flicker (5/10 patients). Vertical gratings were less effective in detecting visual abnormality: the corresponding figures were 3/20 (3/10), 1/20 (1/10), and 1/20 (1/10). No patient showed abnormally high contrast sensitivity in any situation. In total, 6/10 patients had abnormal contrast sensitivity.

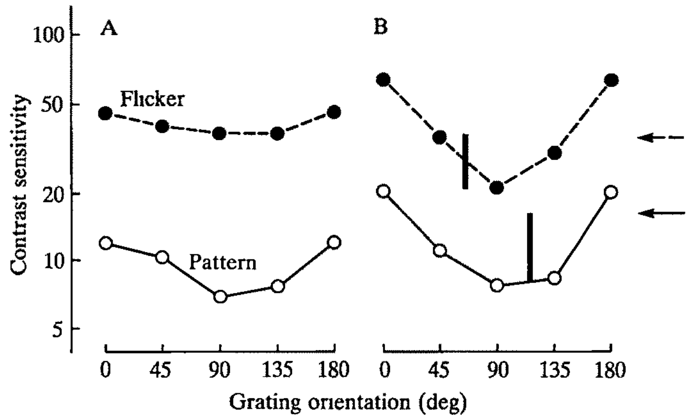

FIG. 1. Effect of orientation on visual contrast sensitivity. Ordinates plot contrast sensitivity for flicker perception (filled symbols) and for pattern perception (open symbols) versus grating orientations (abscissa) Vertical is 0 deg and 180 deg on the abscissa and horizontal is 90 deg. The vertical bars show the upper normal limits for orientational tuning and the horizontal arrows show lower normal limits for absolute sensitivities (99% limits). The grating had a spatial frequency of 2 c/deg and was counterphase modulated at 8 Hz. Case 1; A, left eye, B, right eye.

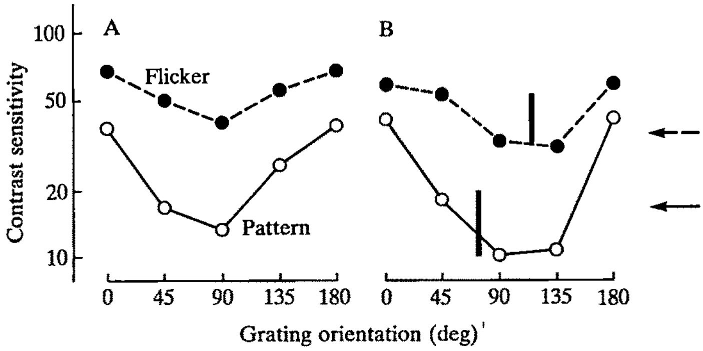

FIG. 2. As for fig. 1. *Case 2*, A, left eye, B, right eye.

Parkinsonian Patients: Orientational Tuning of Pattern and Flicker Sensitivities

Abnormal orientation selectivity was seen in 50% of patients. Detailed findings were: 7/20 eyes (5/10 patients) showed orientation selectivity for either pattern or flicker; 6/20 eyes (5/10 patients) for pattern; 5/20 eyes (4/10 patients) for flicker; 4/20 eyes (4/10 patients) for both pattern and flicker. These findings are illustrated in figs 1 and 2 where the orientation selectivities of pattern and flicker sensitivities are plotted for 2 patients. The two vertical bars indicate upper normal limits (99%) for the orientational tuning ratios of pattern and flicker sensitivities. Orientational selectivity for both pattern and flicker were outside normal limits in the right eye of Case 1 (fig. 1), though within normal limits for the left eye. Control limits (99% confidence) for absolute sensitivity to pattern and flicker are indicated by the two horizontal arrows in fig. 1. The arrows show that, although the left eye was not significantly orientation-selective, absolute sensitivity to pattern was well below normal limits for horizontal gratings, and flicker sensitivity was borderline; both were well below normal limits in the right eye. The right eye is an example of absolute sensitivity for both pattern and flicker being well below normal limits for horizontal gratings, though within normal limits for vertical gratings. Fig. 2 shows that orientational selectivity for pattern was markedly abnormal in both left and right eyes of Case 4; orientation selectivity for flicker was abnormal in the right eye, while the left eye was just within control limits for orientational selectivity and also for absolute sensitivity. Both eyes further illustrate the point that absolute sensitivity can be abnormal for horizontal gratings while being within normal limits for vertical gratings.

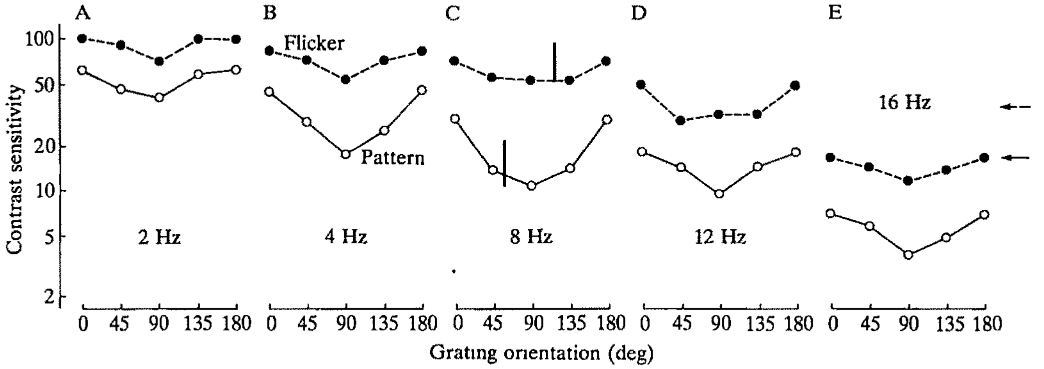

FIG. 3. Effect of temporal frequency on visual contrast sensitivity. Orientational selectivity curves as in fig. 2 are shown for temporal frequencies of 2, 4, 8, 12 and 16 Hz Right eye of *Case 2* The horizontal arrows and error bars apply for 8 Hz. The data for figs 2 and 3 were obtained in different sessions.

Parkinsonian Patients: Effects of Temporal Frequency on Orientation Tuning

Next we investigated in 2 patients whether orientational tuning depended on the temporal frequency of the grating stimulus. Fig. 2B shows orientational tuning for the right eye of Case 2 at a temporal frequency of 8 Hz; fig. 3 compares the orientational tuning for this same eye at frequencies of 2, 4, 8, 12 and 16 Hz, and fig. 4 shows similar data for Case 4. Clearly, the effects of temporal frequency were not the same in the 2 patients: compare the fig. 3 data for Case 2 with corresponding data for Case 4. Pattern sensitivity behaved similarly for both patients, but flicker sensitivity behaved quite differently. Fig. 5 brings out this point. Fig. 5A shows that the orientational tuning of pattern sensitivity was stronger at 4 Hz and 8 Hz than at higher and lower frequencies for both Case 2 (filled symbols) and Case 4 (open symbols). For flicker sensitivity, on the other hand, temporal frequency had quite different effects on orientational tuning for both patients; for Case 4 the orientational tuning of flicker sensitivity was greatest at 2 Hz, and progressively fell as temporal frequency

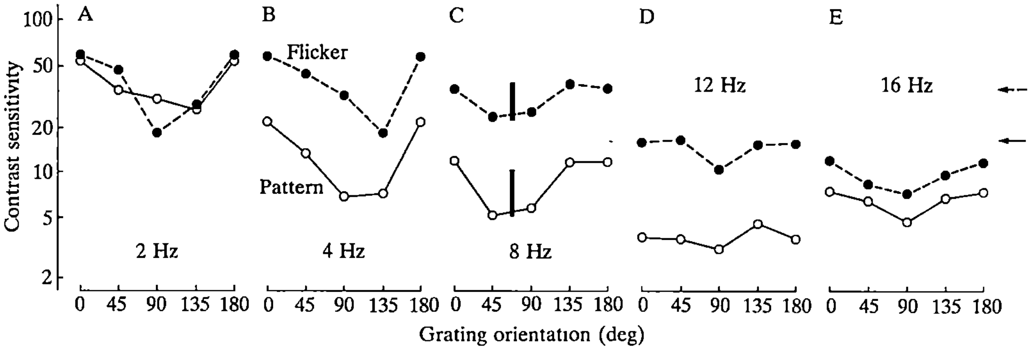

FIG. 4. As for fig. 3. *Case 4*.

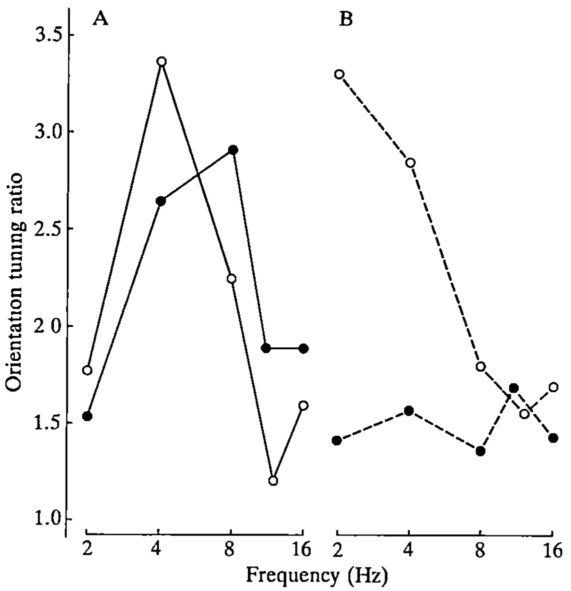

FIG. 5. Data of figs 3 and 4 replotted to bring out the effect of temporal frequency (abscissa) on orientational selectivity (ordinates). Closed symbols show data for *Case 2* and open symbols for *Case 4*. The orientation tuning ratio is defined as the ratio of the highest to the lowest contrast sensitivity among the four grating orientations. A, pattern, B, flicker.

was increased (fig. 5B, open symbols), while for Case 2, orientational tuning for flicker was comparatively weak, and varied little with temporal frequency (fig. 5B, closed symbols).

A less unexpected observation was that raising temporal frequency from 2 to 16 Hz caused a progressive overall loss of pattern sensitivity and flicker sensitivity fell off from above 4 to 8 Hz; these observations have been well documented in control subjects (Kulikowski and Tolhurst, 1973; Braddick *et al.*, 1978).

Visual Fields for Patients with Parkinson's Disease

Conventional Bjerrum screen campimetry was used to record visual fields for Cases 1 (fig. 6A) and 4 (fig. 6B) using standard high-contrast white targets on a black background. Blind spots were identified using a 20 mm diameter (1.1 deg) target.

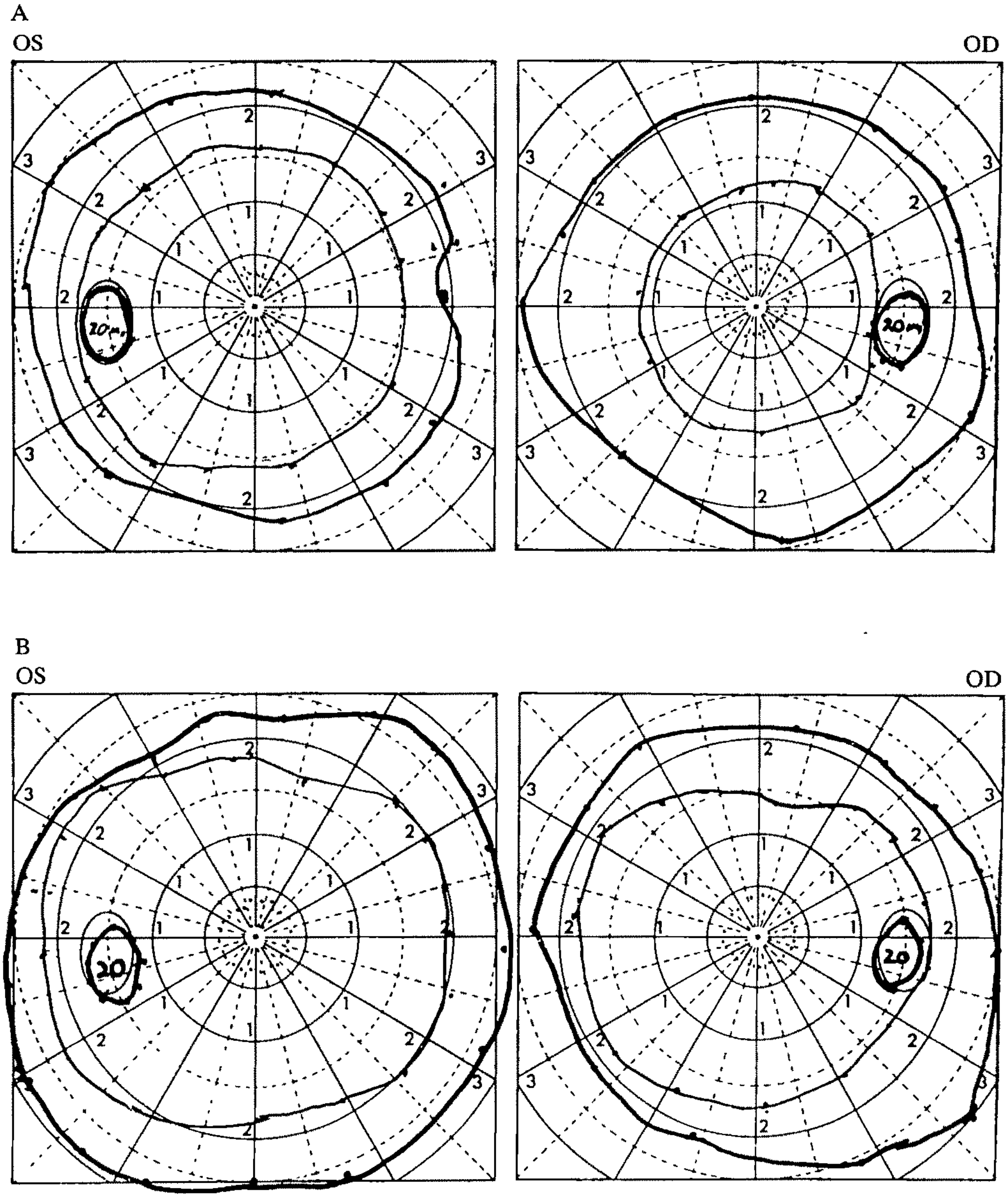

FIG 6. Bjerrum screen fields for *Cases 1* (A) and *4* (B). The outer isoptre is for a 2 mm test target, and the inner for a 1 mm target. Viewing distance was 1 m. The numbers refer to eccentricity· 1 indicates 10 deg, 2 20 deg and 3 30 deg.

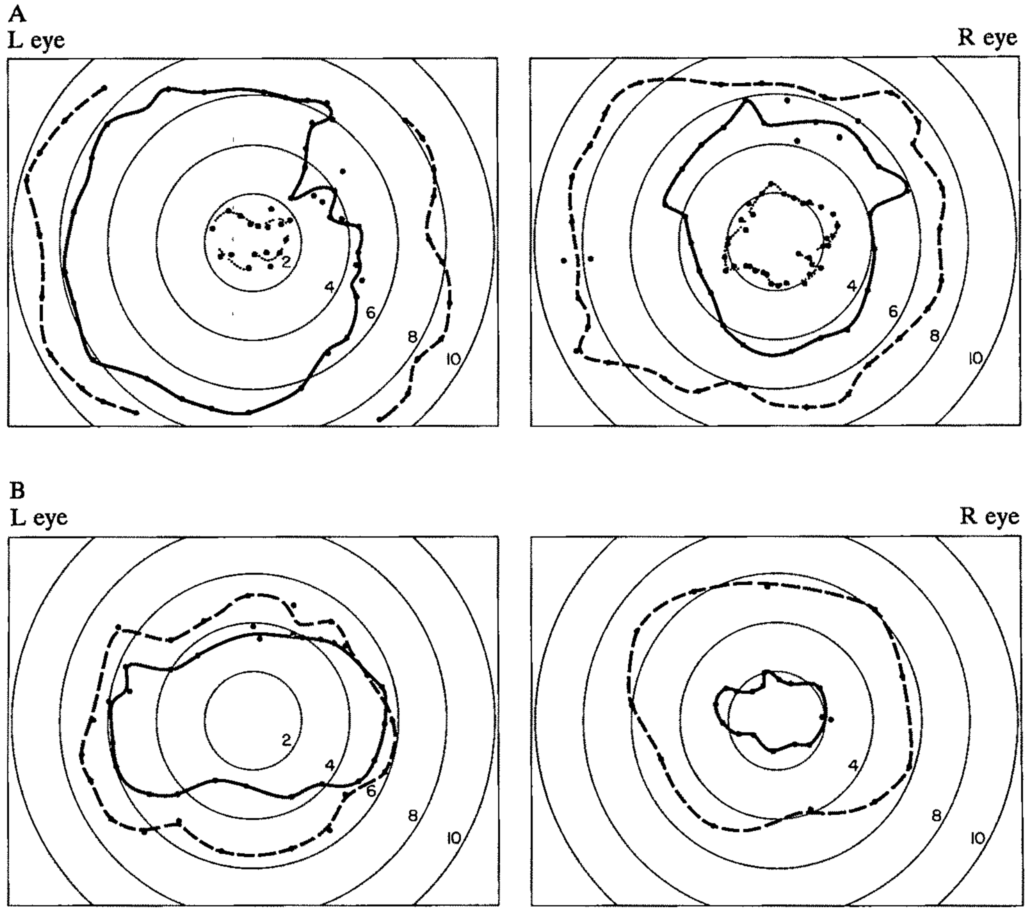

FIG. 7. Low-contrast visual fields for *Cases 1* (A) and *4* (B). The dashed line is for a target of incremental contrast 28%, the continuous line for 18% contrast and the dotted line for 11% contrast. Numbers refer to the radii in degrees of the concentric circles. The target was a blurred spot subtending approximately 0.25 deg.

The outer isopter is for a 2.0 mm (0.11 deg) test target, and the inner isopter is for a 1.00 mm (0.05 deg) test target. In addition, a careful search was made for small scotomata in the central visual field using the 1 mm target; each of the small dots within 5 deg of the central fovea indicated a test site: no small scotomata were found. Visual fields were normal for both patients. Isopters were slightly constricted in the right eye relative to the left in Case 1 (fig. 6A), but the Bjerrum fields provided no hint of explanation for the orientation tuning shown in figs 1 and 2; no horizontal/vertical asymmetry at all was evident for either patient.

Visual fields were also recorded using a different technique. Rather than using conventional small high-contrast sharp-edged targets, we used a large low-contrast blurred test target. Fields for Cases 1 and 4, respectively, are shown in figs 7A and B. The numbers mark the radii in deg of the concentric circles; note that fig. 7 shows isopters extending to only 10 deg eccentricity, while the Bjerrum fields in fig. 6 extend to a radius of 30 deg. The dotted line is for a contrast of 11%, the continuous line for 18% and the dashed line for 28%. A comparison of figs 7 and 6 shows that the low-contrast and high-contrast fields were not equivalent. Low-contrast isopters for Case 4 were more compressed than for Case 1 in fig. 7, while the opposite was the case for the high-contrast isopters of fig. 6. Although the innermost low-contrast isoptres do show some vertical compression for both left and right eyes of Case 4 (fig. 7B), it seemed unlikely that this was related to the orientational tuning of grating sensitivity shown by this patient (fig. 2) because similar orientational tuning was observed in the right eye of Case 1 (fig. 1B) who did not show vertical compression of the innermost low-contrast isopter (fig. 7A, OD); nevertheless, we went on to explore the effect of artificial field loss upon the orientational tuning of grating sensitivity.

TABLE 2 CONTROL DATA FOR HIGH, INTERMEDIATE AND LOW-CONTRAST LETTER CHARTS FOR A GROUP OF 15 SUBJECTS (30 EYES) OF MEAN AGE 60.5 YRS (RANGE 43–75)

	High-contrast chart (84%) *A*	*Intermediate-contrast chart (25%)* *B*	*Low-contrast chart (7%)* *C*	*A–C*
Mean	8.4	7.1	4.9	3.5
SD	1.1	1.1	1.1	0.8
Upper limit	11.2	9.8	7.7	5.4
Lower limit	5.5	4.4	2.1	1.6

Visual Field Restriction and Orientational Tuning of Grating Contrast Sensitivity in Control Subjects

Three control subjects set flicker and pattern sensitivities for vertical and horizontal gratings while viewing the 3.5 deg diameter full-field stimulus, and with the field restricted to a 1.5 deg horizontal slit and also to a 1.0 deg horizontal slit. Although the visual field restriction did depress horizontal sensitivity relative to vertical sensitivity, the effect was considerably less than the orientational tuning seen in patients. For the most severe 1.0 deg field restriction, the changes in the balance of horizontal to vertical sensitivities were as follows: for flicker threshold the 1.0 deg restriction altered the balance by −11%, +53% and +36%, respectively, for the 3 subjects, and for pattern threshold the balance changed by +48%, +35% and +37%. (Positive signs mean that horizontal sensitivity fell with respect to vertical sensitivity.) Compare this with fig. 1 where, even with full-field stimulation, Case 1 had a +200% asymmetry for flicker and a +165% asymmetry for pattern, and with fig. 2 where Case 4 had a 310% asymmetry for pattern. But, of course, figs 6 and 7 show that Cases 1 and 2 did not by any means have field defects as severe as those mimicked by our horizontal slit. It seems, therefore, that field defects played at most

TABLE 3. LETTER CHART RESULTS

		Letter contrast			
		84%	*25%*	*7%*	
Case	*Eye*	*A*	*B*	*C*	*A–C*
1	R	8.4	7.5	4.1	4.3
	L	8·8	7.7	5.3	3.5
2	R	8.3	7.0	4.1	4.2
	L	7.8	6.5	3.4	4.4
3	R	6.7	4.8†	3.1	3.6
	L	7.8	6.4	2.3†	5.5*
4	R	8.3	7.1	3.9	4.4
	L	8.1	7.1	4.0	4.1
5	R	7.8	6.9	4.3	3.5
	L	7.7	7.5	4.7	3.0
6	R	7.1	6.1	3.1	4.0
	L	7.5	6.4	3.1	4.4
7	R	6.7	6.7	3.7	3.0
	L	6.5	6.4	3.4	3.1
8	R	7.7	5.5	2.5†	5.2†
	L	8.3	6.3	2.6†	5.7*
9	R	9.0	8.0	5.0	4.0
	L	8.0	7.0	5.0	3.0
10	R	8.3	7.3	4.3	4.0
	L	9.7	7.4	4.8	4.9

† Greater than 2.0 SDs. * Greater than 2.5 SDs.

a minor role in the orientational selectivity of visual sensitivity shown in figs 1 and 2. A further argument is that the 2 eyes whose visual pathway abnormality was detected by the letter chart test (asterisked in Table 3, columns A–C) were both close to or better than 6/6 Snellen acuity (Table 3, column A), but were unable to read line 3 of the 7% letter chart (Table 3, column C). In other words, these eyes could read high-contrast letters subtending 5 min of arc, but could not read low-contrast letters subtending 17 min of arc so that the visual abnormality existed within a visual field area less than 0.3 deg in diameter.

Visual Acuity and Low-contrast Letter Chart Results in Control Subjects and in Parkinsonian Patients

The group of 15 control subjects was tested with three letter charts. Visual acuities were recorded with a standard high-contrast (84%) Snellen-type chart and reduced-contrast performance was obtained with intermediate-contrast (25%) and low-contrast (7%) charts. Reading scores were calculated as described in Methods. Means, SD, and normal limits are summarized in Table 2. Means were higher and intersubject variability greater than we found for previous control groups (Regan and Neima, 1983, 1984*b*). Possibly this was due to the considerably higher average age of the present control group.

Table 3 shows letter chart results for the 10 parkinsonian patients. Results more than 2.5 SD and 2.0 SD from the control mean are marked, respectively, thus * and †. Visual acuity for all patients (20 eyes) was within control limits, and was 6/6 (line 8) or better for 10 eyes. At the 2.5 SD level, 2 patients (Cases 3 and 8) showed the abnormal difference between high-contrast and low-contrast performance (rightmost column A–C) that is indicative of visual pathway abnormality; one of these patients had better than 6/6 acuity and the other better than 6/7.5.

DISCUSSION

The Specificity of Visual Sensory Loss in Parkinson's Disease

It has been known for several years that visual evoked potentials are delayed in some patients with Parkinson's disease (Bodis-Wollner and Yahr, 1978), but until recently visual sensory loss was not associated with the disease because, as confirmed here, clinical test results are not abnormal for the age group: neither depressed visual acuity nor visual field loss are characteristic of Parkinson's disease. Visual sensory loss can be detected by a simple test comprising low-contrast letter charts in the form of printed cards (Regan and Neima, 1984*b*), and this finding is confirmed here using a different set of charts in the form of projected slides. Our new finding is that orientational selectivity is a considerably more effective indicator of visual sensory loss in parkinsonian patients.

Why is the orientation test so much more effective in detecting visual dysfunction than are clinical visual acuity or visual field tests or even the low-contrast letter chart test? Consider first the standard Snellen-type acuity test. This test assesses a patient's ability to recognize small high-contrast letters, and it is well known that this ability can be spared while the ability to see larger low-contrast test targets is degraded; several visual pathway disorders including, for example, multiple sclerosis (MS) (Regan *et al.*, 1977; Bodis-Wollner *et al.*, 1979; Zimmern *et al.*, 1979) can cause a selective loss of this kind and the loss can be orientation selective (Regan *et al.*, 1980). The differential loss has been attributed to differential susceptibility of neurons sensitive to low and high spatial frequencies (Regan *et al.*, 1977; Bodis-Wollner *et al.*, 1979), although it is not known whether the visual loss is specific for large target size, low target contrast or to a combination of these two variables. Now consider the insensitivity of conventional visual field techniques such as Bjerrum screen and automatic 'Octopus' perimetry. The same argument applies: visual field techniques also assess the ability to see small high-contrast test targets, rather than larger low-contrast test targets. On the other hand, this cannot be the whole story: although blurred low-contrast test targets revealed visual field irregularities that were not shown by high-contrast test targets, these irregularities were not sufficient to account for the orientational tuning shown in fig. 5A.

Although they were clearly superior to the ineffective high-contrast Snellen chart, it is puzzling that our low-contrast letter charts missed 3 of the parkinsonian patients whose visual loss was detected by the orientation test. (In MS the situation seems to be different: the same low-contrast charts are approximately as effective as sinewave gratings (Regan and Neima, 1983; Regan and Maxner, 1986).) One reason may be that, in Parkinson's disease, contrast sensitivity loss may be appreciable only at the rather low spatial frequencies of 2-6 cycles/deg, so that the largest letters in our 7% letter chart were not large enough. For example, the Snellen letter size that corresponds to a 2 c/deg grating is 1.25 deg high (i.e., 20/300, and our largest letter size was only 20/100).

The line width and gap width in a Snellen letter on the 20/20 line is 1 min of arc. In so far as Snellen and grating acuities can be compared, the 20/20 letter size corresponds to a grating spatial frequency of 30 cycles/deg, because each bright or dim bar is 1 min of arc wide in a 30 cycles/deg grating. A 2 cycle/deg grating has a bar width of 15 min of arc, and thus corresponds to Snellen letters on the 20/300 line. Standard test letters are five times higher than the gap and line width, so that letters on the 20/20 line are 5 min of arc high and letters on the 20/300 line are 75 min of arc (1.25 deg) high. Note that, although visual acuity can be tested down to 20/300 merely by moving the patient closer to a standard high-contrast Snellen chart, a low-contrast test cannot be achieved so simply. In order to test vision with letters 1.25 deg high in a patient with normal or near-normal acuity, the letter contrast must be considerably less than the 7% contrast of our slides. Although such ultralow-contrast charts are now available (Paragon Services, Lower Sackville, NS, Canada), they were not available during this study.

A further reason for the total ineffectiveness of low-contrast fields and the comparative ineffectiveness of low-contrast charts may be the temporal tuning of the orientational effect. The orientational tuning of pattern sensitivity was most evident in the temporal range 4 to 8 Hz (fig. 5). It remains to be shown whether the diagnostic yield of low-contrast letter charts in Parkinson's disease is usefully enhanced by temporally modulating letter contrast or luminance and whether the diagnostic sensitivity of low-contrast visual fields is usefully improved by temporally modulating test target contrast or luminance at 2 to 4 Hz.

Site of Visual Damage in Parkinson's Disease

It is known that some patients with Parkinson's disease have visual sensory loss even in the presence of normal visual acuity (Bodis-Wollner *et al.*, 1984; Regan and Neima, 1984*b*). Confirming that point, all 6 patients with abnormal contrast sensitivities had acuities within normal limits set by the age-matched control group. Furthermore, severe contrast sensitivity abnormality was shown by Cases 1 and 4 (4 eyes) whose acuities were 20/20 or better. These findings imply that the responsible pathophysiology was neural rather than optical (i.e., front-of-the-eye).

Because of reports that some parkinsonian patients have abnormally large visual evoked potentials (Ehle *et al.*, 1982) and abnormally high sensory contrast sensitivity (Bodis-Wollner *et al.*, 1984) we checked for abnormally high contrast sensitivities, but failed to find this in any instance. We did not measure the effect of temporal frequency on absolute contrast sensitivity in our patient group, so cannot compare our temporal tuning data with the finding of Bodis-Wollner *et al.* (1984) that absolute sensitivity loss for vertical gratings is most pronounced near 4 to 8 Hz, although we did find orientational tuning for pattern to be maximal near 4 to 8 Hz.

Our present findings on the effects of temporal frequency on the orientational tuning of visual sensitivity may offer some hint as to the site of the responsible visual pathophysiology. First, we put together the following three findings: (1) pattern sensitivity depended on grating orientation; (2) the orientation dependence was greater at temporal frequencies of 4 to 8 Hz than at higher and lower frequencies (fig. 5A); and (3) high spatial frequencies were spared. Because orientation-sensitive neurons are not found peripheral to the primary cortex in primates, our previous finding of orientation-dependent visual loss in patients with MS led us to implicate orientation-selective cortical neurons in that disease (Regan *et al.*, 1980). Following the same reasoning, our present finding of orientation-dependent visual loss in patients with Parkinson's disease leads us to implicate orientation-selective cortical neurons in the visual dysfunction experienced by parkinsonian patients.

One possible explanation for the selective loss of sensitivity to horizontal gratings is based on the finding that in visual cortical area V2 in the baboon there is a marked bias for neurons to prefer vertically orientated stimuli, while in area V1 there is a roughly similar preference for horizontal and vertical orientations (Kennedy *et al.*, 1985) (pointed out to us by G. Orban). This is consistent with the suggestion that patients with a selective loss of horizontal sensitivity have experienced selective damage to the human equivalent of V1 striate cortex, leaving V2 as the main contributor to contrast sensitivity.

A second physiological finding that may be relevant is that, in Old World primates, the afferents from the parvocellular and magnocellular layers of the lateral geniculate body are partially segregated at their zones of termination in lamina IV of the striate cortex (Hawken and Parker, 1984). Neurons in the parvocellular layers may be important in visual acuity because they respond to much higher spatial frequencies (up to 40 c/deg; Derrington and Lennie, 1984) than do neurons in the magnocellular layer (Shapley *et al.*, 1981; Kaplan and Shapley, 1982; Derrington and Lennie, 1984). If it is valid to extrapolate these monkey data to the human, we can conclude that neurons in the parvocellular layers were comparatively unaffected in our parkinsonian group, because visual acuity was spared (*see* Results). Although neurons in the magnocellular layers do not respond to the high spatial frequencies that excite neurons in the parvocellular layers they are, nevertheless, much more sensitive than parvocellular neurons at low spatial frequencies (Shapley *et al.*, 1981; Kaplan and Shapley, 1982; Derrington and Lennie, 1984) so that they are capable of providing a dominant contribution to visual contrast sensitivity at low spatial frequencies, though this may be offset to some extent by their lower numbers. Furthermore, the sensitivity of magnocellular layer neurons falls off below about 4 Hz and above about 15 Hz (Derrington and Lennie, 1984) so that our 2 c/deg, 8 Hz grating would be a near-optimal stimulus for these cells; note also in fig. 5A the fall-off of the orientational tuning ratio at high and low temporal frequencies. According to this line of argument, selective damage to cells in the retina-magnocellular LGN layer-cortical pathway would result in a selective loss of contrast sensitivity to gratings of low spatial frequency modulated at around 8 Hz temporal frequency. Perhaps postmortem investigation of the LGNs of parkinsonian patients might bring to light a selective susceptibility within the different layers.

Continuing this line of argument, some neurons in the magnocellular layer receive predominant input from retinal X cells, while others are chiefly driven by retinal Y cells (Hawken and Parker, 1984). Comparing the two kinds of magnocellular cell, those that receive X input are relatively more sensitive over the range 1 to 2 c/deg (Kaplan and Shapley, 1982). It is tempting to link this differential sensitivity of magnocellular X and Y neurons in monkey with the differential effect of Parkinson's disease on flicker and pattern sensitivity in humans (*see* figs 1–4); flicker sensitivity would be relatively affected by a preferential loss of magnocellular X cells, and pattern sensitivity would be relatively affected by a preferential loss of magnocellular Y cells.

Turning to possible mechanisms of visual loss, dopamine-sensitive cells are known to exist in the human retina (Frederick *et al.*, 1982) and dopamine depletion is known to slow transmission in rat retina (Dyer *et al.*, 1981); it has been suggested that the dopaminergic deficiency associated with Parkinson's disease might well result in peripheral visual dysfunction (Bodis-Wollner *et al.*, 1982).

Paralleling previous studies in MS (Regan *et al.*, 1980; Camisa *et al.*, 1981; Kupersmith *et al.*, 1984), we find that some patients experience orientation-selective *monocular* loss of contrast sensitivity. This finding is difficult to reconcile with reports that, even though one eye may inhibit and the other excite, orientation-selective cortical neurons generally receive inputs from both eyes.

Finally, we should note an intriguing parallel between the pattern of visual loss in patients with Parkinson's disease and patients with MS. Of 18 MS patients whose foveal vision was tested with a 2 cycles/deg 8 Hz grating, 12 patients showed orientational tuning for flicker and/or pattern, and in all cases horizontal sensitivity was least and vertical sensitivity greatest, as reported here for parkinsonian patients (Regan and Maxner, 1986). Ten of the 12 MS patients had acuity of 20/25 or better. The effect of temporal frequency was investigated in one MS patient; her results were similar to those of fig. 5 (filled symbols). It would indeed be curious if the rather specific pathophysiology suggested above does prove to be shared by two so dissimilar disease entities as MS and Parkinson's disease.

Differential Loss of Pattern and Flicker Sensitivities

The hypothesis (Keesey, 1972; Kulikowski and Tolhurst, 1973; Tolhurst, 1973; Bodis-Wollner and Hendley, 1979) that the existence of separate thresholds for pattern and for flicker or motion sensation implies two somewhat separate neural mechanisms has recently been challenged: some authors claim that the two thresholds correspond to nothing more than two levels of excitation of the same mechanism (Burbeck, 1981; Derrington and Henning, 1981).

Our present findings bear on this controversy. Fig. 5 shows a double dissociation: (1) orientation tuning of pattern sensitivity can exist in the absence of orientation tuning for flicker/motion sensitivity (fig. 5, filled symbols); (2) both pattern and flicker/motion sensitivity may be tuned to orientation, but with quite different temporal dependencies (fig. 5, open symbols). This double dissociation between sensitivity to pattern and to flicker/motion is difficult to reconcile with a single-mechanism hypothesis, but is consistent with the idea that, at some point in the visual pathway, pattern and flicker/motion signals are sufficiently separate or physically different that one signal can be impaired relative to the other (Essock and Lehmkuhle, 1982; Murray *et al.*, 1983; Brussell *et al.*, 1984; Regan and Neima, 1984*c*).

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STRETCH AND VIBRATION REFLEXES OF WRIST FLEXOR MUSCLES IN SPASTICITY

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SUMMARY

The surface electromyographic (EMG) reflex responses of the voluntarily contracting flexor carpi radialis evoked by 'stretch' and by tendon vibration have been compared in patients with spasticity of the upper limb, arising from upper motor neuron lesions, and normal subjects. Reflex responses to 'stretch' comprised increases in EMG activity lasting up to 100 ms which were often divided into 'short' and 'long'-latency peaks. The short-latency responses of spastic patients were increased in size compared with those of normal subjects whereas later activity was commonly reduced or absent. In both groups vibration elicited short-latency, essentially phasic responses with activity falling back to or below the background level within 50 ms despite continuing stimulation. These initial reflex responses were exaggerated in the spastics as compared with the normals. In the relaxed state 'stretch' and vibration either failed to elicit reflex responses in normal subjects or reflexes were of small amplitude; in spastic patients both modes of stimulation regularly evoked well developed responses.

These findings with 'stretch' and vibration, both of which forms of stimulation powerfully excite primary endings of muscle spindles, support the view that group Ia afferent-mediated reflex action is enhanced in spasticity. The observation that the normal long-latency responses evoked by stretch, which have been attributed to the action of spindle group II afferents (Matthews, 1984*a*) additionally excited with this stimulus, are depressed in many spastic patients is consistent with reduced group II effects. Observed abnormalities of stretch reflex behaviour did not readily explain the severity of accompanying spasticity of individual patients.

INTRODUCTION

Spasticity is a common feature of upper motor neuron syndromes. This motor disorder is characterized by exaggerated tendon jerks and a velocity-dependent increase in muscle tone and is generally held to result from enhancement of stretch reflex activity. In accordance with this view, electromyographic (EMG) analyses have confirmed that the short-latency (MI) reflexes of many spastic patients elicited during application of moderately prolonged stretch were unusually large (Lee and Tatton, 1975, 1978; Marsden *et al.*, 1977; Chan *et al.*, 1979; Berardelli *et al.*, 1983). In contrast, long-latency (M2-M3) response components were commonly found

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to be reduced compared with the normal or absent. Such decreases in long-latency stretch reflexes in spasticity seem, at first sight, surprising, especially since the occurrence of any such delayed responses might be expected to help to support resistance to displacement and to contribute to muscle tone.

Thus an appreciation of the mechanisms normally responsible for the delayed, as well as early, components of the stretch reflex assumes particular significance in attempting to understand the causes of altered muscle tone, including spasticity. The origin of the long-latency stretch reflex is controversial and several mechanisms have been proposed for its generation. The 'transcortical' (Phillips, 1969; Marsden *et al.*, 1972), 'resonance' (Eklund *et al.*, 1982) and 'Group (Gp) II' (Matthews, 1984*a*) hypotheses each attribute late reflex components to sensory inflow arising from muscular receptors. According to the first two views, later reflex components result from activity in Gp Ia afferents from spindle primary endings, whereas the third attributes such responses to the smaller, more slowly conducting Gp II fibres from spindle secondary endings. Alternatively, cutaneous and/or joint afferents, activated concurrently by the mechanical stimulus, may evoke separate 'long-latency' reflexes (*see* Jenner and Stephens, 1982; Darton *et al.*, 1985; Deuschl *et al.*, 1985; Marsden *et al.*, 1985) which could supplant or supplement those of muscle origin. The reduced long-latency stretch reflexes of spasticity may thus potentially be explained in terms of abnormal Gp Ia, Gp II or cutaneous reflex action.

The present investigation focuses on the reflex contributions of Gp Ia and II muscle afferents in spastic and normal subjects, studied by comparison of responses to stretch and vibration. This approach was developed by Matthews (1984*a*) in experiments on the normal long flexor of the human thumb. Its underlying rationale is that stretch excites both spindle primary and secondary endings powerfully whereas vibration is a relatively selective stimulus for the primary endings, including in man (Burke *et al.*, 1976*a*, *b*). Therefore if all reflex components depend upon Gp Ia activity, broadly similar responses to stretch and vibration may be expected; if differences are found they presumably arise from the added excitation of Gp II with stretch. The situation in spasticity follows as a corollary: alterations in any reflex component which can be attributed to Gp II action in the normal subject are most readily interpreted as arising from derangement of Gp II influences in spasticity. The wrist flexor muscles have been used since their stretch reflexes have already been studied in depth (Verrier *et al.*, 1984) and they may be assumed to be under significant cerebral cortical control. Some of the present findings with vibration have been reported in abstract form (Cody *et al.*, 1983).

METHODS

Subjects

The study was made on 23 patients: 12 with multiple sclerosis, 3 with cervical cord lesions, 3 with amyotrophic lateral sclerosis (ALS), 3 with cerebral hemisphere stroke, 1 with a cerebral hemisphere tumour and 1 with a pontine tumour. Patients with severe weakness at the wrist were avoided, as were those who were unable to sustain a steady voluntary contraction of about 20% of their individual maximum or whose disability seemed likely to preclude their cooperation in our experimental procedures. The clinical features of the patients, subdivided according to the nature of their neurological disease, are as follows.

Multiple sclerosis (*MS*). In each of the 12 patients the diagnosis was 'definite' (Schumacher *et al.*, 1965; Rose *et al.*, 1976). All had tendon jerk hyperreflexia and a degree of spastic paresis in the arm studied. In 2 patients this was accompanied by sensory disturbance; in 1, tingling of the fingers was present and in the other, light touch, joint position and pain sensation in the upper limb was impaired. The range of additional motor signs varied between individual patients: 2 were monoparetic, 3 hemiparetic and 7 tetraparetic. One of the patients with tetraparesis showed signs of early cerebellar involvement and a slight intention tremor of the arm.

Cervical cord lesions. Two of the 3 patients had cervical spondylotic myelopathy. Myelograms showed intervertebral disc protrusions at several levels. In both these patients, the pattern of tendon reflexes in the upper limb (exaggerated triceps jerks, depressed biceps and brachioradialis jerks) suggested a cord lesion at C5–6. The distribution of spastic paresis and tendon jerk hyperreflexia varied between the 2 patients; in 1, it was confined unilaterally to the upper and lower limbs whereas in the other it was present in all four limbs. The former patient had minimal sensory disturbance while the latter had loss of light touch and position sense in all extremities. The third patient, in whom corrective surgery for spinal bifida had been performed in childhood, had a small meningomyocele at C4 with cavitation of the cord below this level. A spastic tetraparesis and generalized tendon jerk hyperreflexia were present with weakness and wasting in C5 distribution. Joint, position sense was lost in the fingers and toes.

Amyotrophic lateral sclerosis. The patients each had predominantly upper motor neuron signs, including spastic tetraparesis and generalized tendon jerk hyperreflexia. In none was there evidence of lower motor neuron degeneration on clinical examination although in all, needle EMG recording indicated widespread low level denervation. Sensory function was intact in all 3 patients.

Cerebral hemisphere stroke. Each of the 3 patients was hemiplegic, and increased tendon jerk reflexes and tone were present in both upper and lower limbs of the affected side. In all, weakness was greater in the leg than the arm and extensor plantar responses were present. Two of the patients had a marked unilateral sensory disturbance, involving both upper and lower limbs while in the third, abnormalities of sensation were mild and largely restricted to the lower limb.

Cerebral hemisphere tumour. A parietal tumour, believed to be metastatic renal carcinoma, was identified by CT scanning. The patient reported clumsiness of one arm, unsteadiness of gait and headache of five days duration. Upper limb motor signs were unilateral and comprised increased tendon jerks and tone, and mild weakness. There was complete loss of position sense in the affected arm.

Pontine tumour. A pontine tumour, believed to be a glioma, was identified by CT scanning. The patient was hemiparetic. Tendon jerk hyperreflexia, moderate spasticity and marked weakness were present in the affected arm.

Patients were each examined by an experimenter (I.T.F. or N.MacD) in whose clinical charge they were. Muscle strength, tone and tendon reflexes were assessed in the upper limb. Strength was classified according to the MRC 0–5 scale. Tone was evaluated on a four point scale: 0, normal; 1, mild; 2, moderate; 3, marked. Reflexes were graded: 0, absent; 1, reduced; 2, normal; 3, increased; 4, markedly increased. The mean age of the patients was 45 yrs ± 3 (SD); 14 were male, 9 were female.

Twenty normal subjects were also studied (mean age 51 ± 5 yrs; 7 male, 13 female); none showed signs of neurological disease. They included 14 subjects who formed an age-matched group of normals in a recent study of stretch and vibration-evoked reflexes in parkinsonism, and whose ranges of responses, measured under similar conditions to those presently used, were compared with that of rigid patients (Cody *et al.*, 1986).

A more detailed account of the techniques used to apply mechanical stimuli, to record EMG activity and to analyse EMG averages has been published previously (Cody *et al.*, 1986).

Application of 'Stretch' and Vibration

'Stretch'. The subject sat and grasped a vertical handle, coupled to a powerful electromagnetic vibrator by an isometric force transducer, so that it lay along the heads of the metacarpals. The arm was pointing forwards and semipronated with the forearm resting on a horizontal support and clamped at its distal end by padded vertical bars. The electromagnetic vibrator operated as a position servo using negative feedback from a linear displacement transducer. Subjects were required to maintain a steady wrist flexor force of about 20% maximum, aided by a visual monitor, or to relax, and were told to ignore any force changes produced by stimulation and neither to resist not to assist movement. 'Ramp and hold' movements of the vibrator were used to dorsiflex the wrist and thereby to 'stretch' flexor carpi radialis. Movements of 10 mm were routinely applied which corresponded to a wrist rotation of approximately 10°. Velocities of displacement were 50, 100, 200 and 300 $mm \cdot s^{-1}$. Stretch, including its rising phase, routinely lasted for 400 ms and was then released at the same velocity. For application of stretch stimuli to the 'relaxed' muscle, the hand was taped firmly to the handle of the mechanical actuator. Thus movements of the vibrator produced corresponding rotations of the wrist joint despite the absence of steady voluntary flexion acting to keep the hand in contact with the vibrator handle.

Sequences of 64 or 128 similar movements were repeated at respective repetition rates of 0.5 and $1.0 \cdot s^{-1}$ to provide blocks of data for averaging.

Vibration. Sinusoidal displacements (peak-peak 0.5-1.0 mm, 123 or 140 Hz) generated by a small electromagnetic vibrator were applied to the tendon of flexor carpi radialis, transcutaneously, about 5 cm above the wrist crease. The vibrator was suspended from a cantilever system and pivoted and counterweighted so as to press against the arm with a constant force of about 2.5 N. The head of the vibrator, attached to its moving element, was a 1 × 1.5 cm plastic block hollowed to fit the tendon. Periods of vibration were normally 400 ms (as for stretch) and were repeated at 0.5 or $1.0 \cdot s^{-1}$ for, respectively, 64 or 128 presentations. Each train of vibration began with a half cycle of release, so that the first inward displacement of the tendon would be of full size, and terminated with a half cycle of release.

Electromyographic recording. Pairs of surface electrodes, 5 cm apart, were placed over the belly of flexor carpi radialis. Signals were filtered (band pass 20 Hz-3 kHz) and rectified (time constant 1 ms) before averaging. EMG was recorded, together with displacement and timing pulses, on a four-channel tape recorder for off-line averaging using different binwidths to improve resolution. EMG recordings were also regularly made from wrist extensor muscles. None of the subjects (normal or spastic) showed appreciable extensor activity either during production of our standard wrist flexor force or when attempting to relax.

Analysis of EMG averages. In order to allow normalization of the averaged responses, areas under the curves were computed using a graphics tablet interfaced to an Apple II computer to digitize selected parts of print-outs of the waveforms. Fractional increases in EMG over background levels (*see* Rothwell *et al.*, 1983) were calculated by first measuring the response area above the prestimulus baseline and then dividing this by the baseline area for an equivalent time period. This method of normalization was applied to minimize any effect of variation of absolute tonic EMG levels between subjects despite production of similar percentages of their individual maximal voluntary effort. It should, additionally, largely compensate for any systematic differences in voluntary power between spastic patients, many of whom had some degree of weakness, and normal subjects.

RESULTS

The principal findings of the present experiments are embodied in the records illustrated in fig. 1. As shown in the upper traces, 'stretch' of the normal, voluntarily contracting flexor carpi radialis, by dorsiflexion of the wrist, evoked its familiar, prolonged electromyographic response subdivided into two main peaks. In the spastic patient, with moderately increased tone, the intitial wave (M1 or short-latency response), commencing at a latency of about 25 ms, is substantially enhanced whereas the later wave (M2 or long-latency response) occurring at about 50 ms is appreciably reduced compared with the normal. The lower traces show the responses elicited at the beginning of 400 ms trains of flexor tendon vibration. Two main features are apparent. First, in both normal and spastic muscles vibration produced essentially phasic reflexes lacking long-latency components in spite of continuing mechanical stimulation; secondly, the short-latency component of the responses of the spastic patient was exaggerated.

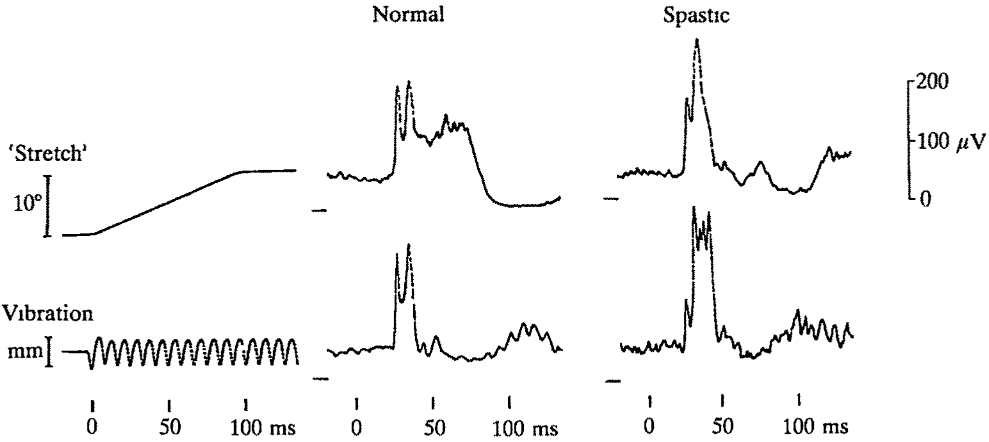

FIG. 1. Comparison of the rectified EMG patterns evoked in flexor carpi radialis by dorsiflexion of the wrist ('Stretch') and by vibration of the flexor tendon (Vibration) in a normal subject and in a patient with moderate spasticity. Subjects maintained a steady wrist flexor torque of about 20% maximal throughout and were required not to respond voluntarily to the stimuli. Sixty-four trials averaged; repetition rate, $0.5 \cdot s^{-1}$. Stimulus waveforms indicate the angular displacement applied to the wrist (*upper*) and vibratory displacement applied to the tendon (*lower*). Zero level EMG is shown by the horizontal bar at the beginning of each record

Fig. 2 shows that these basic features are observed over a range of stimulus strengths and in other subjects. In the normal subject, increasing stimulus strength, by using a higher velocity of stretch or greater amplitude of tendon vibration, evoked larger short-latency responses whilst having more complex effects upon M2 amplitudes.

The series of responses of the spastic patient differed from that of the normal subject in several respects. The short-latency responses, both to vibration and stretch, were more pronounced at low strengths of stimulation and showed larger incremental increases with increasing amplitude of vibration or velocity of stretch. Additionally, it may be noted that long-latency stretch responses were always small, irrespective of the speed of stretch or size of the preceding short-latency reflex.

In order to compare the relative sizes of short and long-latency components between various subjects, we have measured response areas over the periods of 20–40 ms and 50–90 ms. These periods were used for all individuals and for all stimulus parameters so as to avoid any subjective measurement bias that might arise if the values were altered according to the precise features of particular response waveforms. These measurement periods are indicated on the records of fig. 2 and where, as was generally so, they provided adequate samples of the early and late components of response.

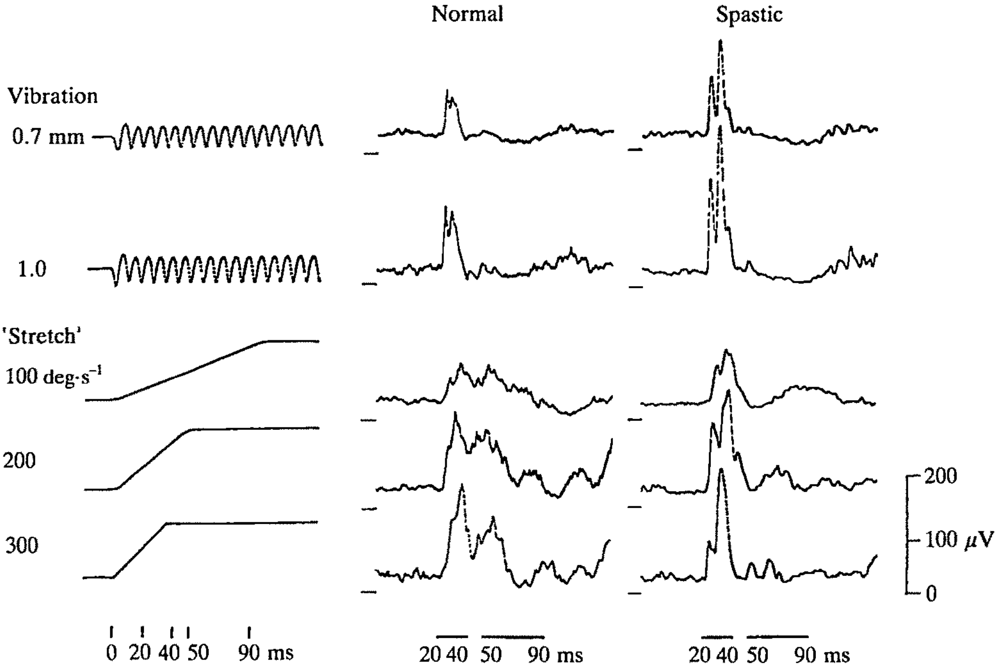

FIG. 2. Effects of varying the amplitude of tendon vibration (*upper*) and velocity of stretch (*lower*) upon EMG reflex responses. The subjects are different from those of fig. 1; the patient had marked spasticity of the upper limb. The bars below EMG records indicate the intervals used for measurement of short and long-latency responses for 100 and 200 deg·s^{-1} stretches.

The impression, gained by inspection of individual records, that stretch and vibration evoked essentially different reflex response patterns, was tested quantitatively for all subjects by measurement of normalized responses over periods corresponding to M1 and M2 intervals. Such measurements also allowed calculation of any correlation between M1 and M2 components. The data of 20 normal subjects for 100 deg·s^{-1} stretch (open symbols) and 0.7 mm vibration (closed symbols) is plotted in fig. 3A. The graph confirms that vibration consistently failed to evoke excitatory EMG responses during the M2 interval, in contrast to stretch, and indeed the EMG activity often fell below background levels during this period.

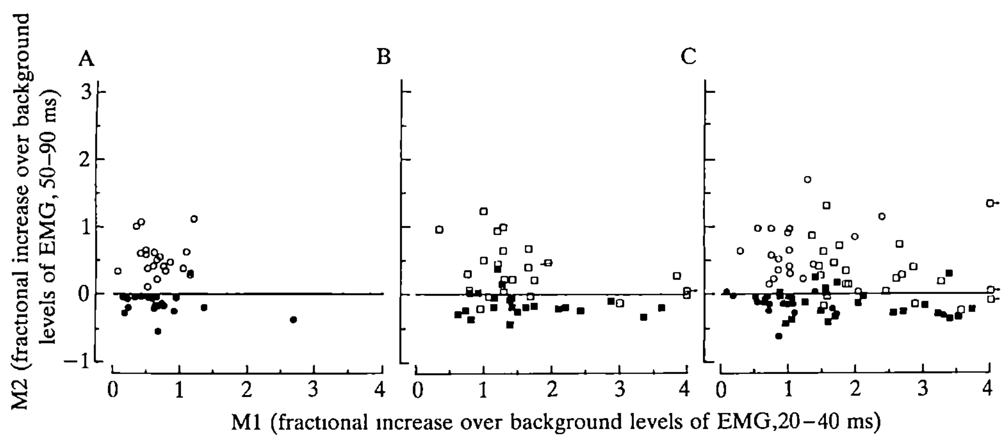

FIG. 3. The relation between the amplitudes of long-latency (M2) and short-latency (M1) responses evoked by stretch (open symbols) and vibration (closed symbols). A, 20 normal subjects, 100 deg·s^{-1} stretch and 0.7 mm vibration. B, patients with spasticity, 100 deg·s^{-1} stretch (23 patients) and 0.7 mm vibration (22 patients). C, both normals (circles) and spastic patients (squares) for 200 deg·s^{-1} stretch (20 normals, 23 patients) and 1.0 mm vibration (20 normals, 22 patients). Response areas, above background EMG levels, have been normalized by dividing by the background level (*see* Methods); activity of an overall area (including background) twice that of the background EMG measured over a similar period yields a scale value of 1, negative values indicate activity below background (e.g. activity of an overall area of one half that of the background yields a scale value of −0 5). M1 responses were measured over the interval 20-40 ms from the onset of the stimulus, and M2 responses over the interval 50-90 ms.

Short-latency responses to both forms of stimulus are distributed over similar ranges so that motoneuronal refractoriness seems unlikely to have been responsible for the absence of long-latency responses with vibration. No consistent correlation between M1 and M2 stretch responses, either positive or negative, was found (Spearman rank correlation coefficient, $r_s = -0.15$, $P = 0.53$). This reinforces the view that refractoriness was not a major factor (if so, a negative correlation might be expected) and that the two responses are largely independent. Corresponding data for 23 spastic patients are presented in fig. 3B. The plot resembles that of the normal subjects in its two main features. First, the distributions of short-latency responses, evoked by stretch and vibration, are comparable. Secondly, vibration was generally ineffective in producing long-latency responses whereas these were seen with stretch in the majority of patients (19/23) and in some cases were moderately well-developed. Again, no significant correlation between the sizes of M1 and M2 stretch responses was found ($r_s = -0.32$, $P = 0.13$). Fig. 3C shows that similar results are obtained with faster stretches (200 deg·s^{-1}) and larger amplitude vibration (1.0 mm) and extends the generality of the findings.

Short-latency Reflex Responses

Two principal questions have been addressed in relation to short-latency reflexes. First, whether, over a range of subjects with varying degrees of reflex responsiveness, a correlation existed between the amplitudes of M1 responses evoked by stretch and vibration. Secondly, whether the short-latency responses of spastic patients differed in amplitude systematically from those of normals.

Correlation of short-latency stretch and vibration responses. The scatter-diagrams of fig. 4 plot the relationship between the amplitudes, measured over the M1 interval, evoked by the two forms of stimulation in spastic and normal subjects. Considering all subjects, both normal and spastic, highly significant correlations between the amplitudes of M1 responses elicited by stretch and by vibration were found for both combinations of stimulus parameters tested (100 deg·s^{-1}: 0.7 mm, fig. 4A; 200 deg·s^{-1}: 1.0 mm, fig. 4B). Spearman rank correlation coefficients were, respectively, 0.71 and 0.73 ($P < 0.00001$). This provides statistical confirmation that when stretch elicited large responses, so also did vibration. Such correlations, additionally, suggest that the short-latency responses produced by the two modes of stimulation may be considered analogous and are probably generated by common mechanisms.

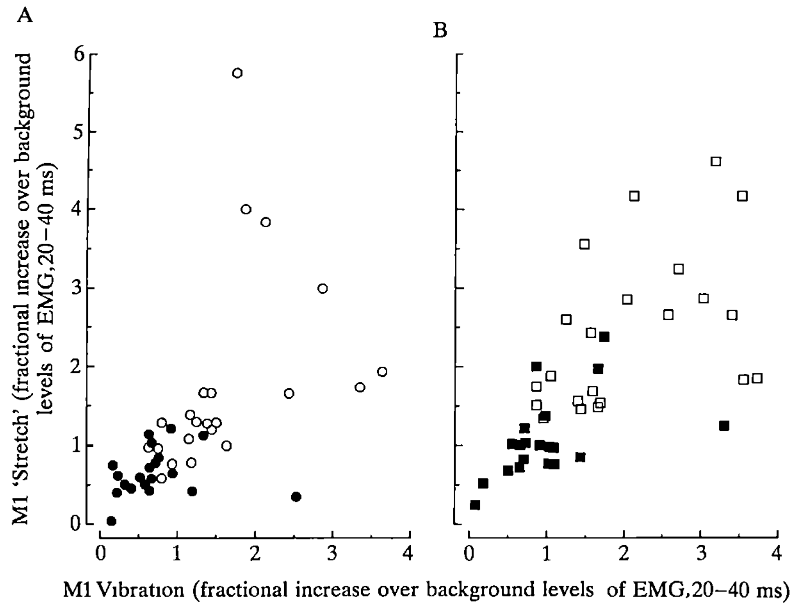

FIG. 4. The correlation between the normalized amplitudes of short-latency responses, measured over the 20–40 ms interval, evoked by stretch (M1 Stretch, ordinate) and by vibration (M1 Vibration, abscissa). A, both normals (●) and spastic patients (○) for 100 deg s^{-1} and 0.7 mm vibration. B, both normals (■) and spastics (□) for 200 deg s^{-1} and 1.0 mm vibration. For both graphs, data points were obtained from 20 normal subjects and 22 patients. Spearman rank correlation coefficients and probabilities that these values differed significantly from zero were· 100 deg·s^{-1}: 0.7 mm; normals and spastics combined, $r_s = 0.71$, $P = 0.00001$; normals, $r_s = 0.28$, $P = 0.24$; spastics, $r_s = 0.77$, $P = 0.00009$; 200 deg·s^{-1}: 1.0 mm; normals and spastics combined, $r_s = 0\ 73$, $P = 0$, normals, $r_s = 0.55$, $P = 0\ 012$; spastics, $r_s = 0\ 53$, $P = 0.012$.

Amplitudes. The histograms of fig. 5A–D compare the amplitudes of normalized short-latency reflexes, elicited at about 20% maximum voluntary contraction, of

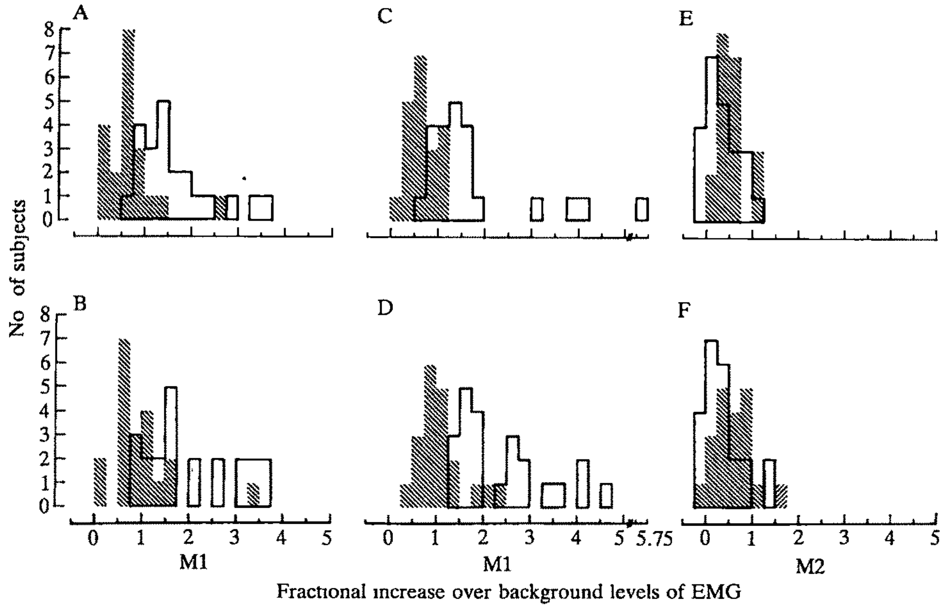

FIG 5. Comparison of the amplitudes of reflex response components elicited in spastic patients (solid line enclosing clear area) and normal subjects (cross-hatched) A, B, M1 responses evoked by vibration; A, 0.7 mm, B, 1.0 mm. C, D, M1 responses evoked by stretch, C, 100 deg·s^{-1}, D, 200 deg·s^{-1}. E, F, M2 responses evoked by stretch, E, 100 deg s^{-1}, F, 200 deg·s^{-1}. Short-latency responses, elicited both by stretch and by vibration, were on average increased in spastic patients, whereas their long-latency stretch responses were on average decreased.

spastic and normal subjects, measured over the standard M1 interval, for two amplitudes of vibration and two speeds of stretch (100 deg·s^{-1} and 0.7 mm; 200 deg·s^{-1} and 1.0 mm).

On average the short-latency responses of spastic patients were greater than those of normal subjects for each parameter of stimulation (Mann-Whitney U test, $P < 0.001$; *see* Table 1). Although some degree of overlap occurred for each of the pairs of distributions, many spastic subjects had responses that were well beyond the normal range.

The background levels of EMG associated with each stimulus parameter were, as calculated from pooled data, on average slightly lower for the spastic than normal subjects but none of the differences was statistically significant (Mann-Whitney U test, $P > 0.1$). The greater amplitudes of normalized short-latency responses of the spastic patients could not, therefore, have arisen fortuitously, as might have occurred if both their tonic levels of EMG had differed systematically from those of normal subjects and the relationship between response amplitudes and background activities had been nonlinear.

In 10 patients and in 6 normal subjects, reflex responses to stretch (300 deg·s^{-1} triangles) and vibration (0.7 mm) were studied while subjects were instructed to exert no voluntary wrist flexor torque and to allow both their wrist flexor and extensor muscles to relax fully. Each of the spastic patients, tested in this situation, had well-developed short-latency responses both to stretch and to vibration. The stretch responses of normal subjects were invariably small, in comparison with those of the spastics, as were their vibration reflexes (which in 2 of the 6 subjects were indistinguishable from the baseline). M1 responses, normalized with respect to background EMG, elicited by both modes of stimulation, were larger for the spastic patients than for the normal subjects (Mann-Whitney U test, $P < 0.001$).

TABLE 1. AMPLITUDES OF SHORT-LATENCY AND LONG-LATENCY REFLEX RESPONSES IN SPASTIC AND NORMAL SUBJECTS*

		M1		*M2*	
		Spastic	*Normal*	*Spastic*	*Normal*
Stretch	100 deg·s^{-1}	1.75 ± 0.26	0.68 ± 0.07	0.36 ± 0.08	0.54 ± 0.06
		($P = 0.000004$)		($P = 0.048$)	
	200 deg·s^{-1}	2.41 ± 0.21	1.10 ± 0.12	0.35 ± 0.09	0.60 ± 0.10
		($P = 0.000003$)		($P = 0.045$)	
Vibration	0.7 mm	1.61 ± 0.17	0.71 ± 0.12		
		($P = 0.00002$)			
	1.0 mm	2.07 ± 0.20	0.99 ± 0.15		
		($P = 0.001$)			

* Mean values (± SEM) of normalized responses elicited in the voluntarily contracting muscle (about 20% of individual maximum). Levels of statistical significance from Mann-Whitney U test. Stretch data from 23 spastic and 20 normal subjects; vibration data from 22 spastic and 20 normal subjects.

The amplitudes of short latency responses of the spastic patients evoked by 'stretch' and vibration were positively correlated with the clinical rating of tendon jerk hyperreflexia (measured at the wrist in the relaxed state). This relationship was tested in the voluntarily contracting muscle using two velocities of stretch (100 deg·s^{-1} and 200 deg·s^{-1}) and two amplitudes of vibration (0.7 mm and 1.00 mm) and in the 'relaxed' muscle using 300 deg·s^{-1} stretches and 0.7 mm vibration. In each case the correlation (Spearman rank correlation coefficient) was significant at the 5% level.

Long-latency Reflex Responses

In contrast to the enhancement of their short-latency reflexes, the amplitudes of long-latency stretch responses of spastic patients, measured over the M2 interval, were on average lower than those of normal subjects (Mann-Whitney U test, $P < 0.05$, *see* Table 1). This finding is illustrated in the histograms of fig. 5E, F, which compare the sizes of M2 responses of spastics and normals for two speeds of stretch. However, the distributions of the two groups show appreciable overlap.

The general reduction in M2 responses amongst the spastic sample resulted, at least in part, from their long-latency peaks ending earlier (as measured by EMG returning to prestimulus levels) than in normals. This effect was particularly marked at the higher speed of stretch. Mean times of termination of M2 excitatory responses, evoked by 200 deg·s^{-1} stretches, for spastic and normal groups were 72 ± 3 ms (SEM) and 85 ± 2 ms which differed highly significantly (Mann-Whitney U test, $P = 0.0008$). Corresponding values for 100 deg·s^{-1} stretches were 89 ± 3 ms and 93 ± 2 ms ($P = 0.27$). Visual inspection of individual records (*see* figs 1, 2) suggested that the M2 responses of spastic subjects, also tended to be slightly delayed in onset. However, because they blended with preceding M1 components, this point could not be tested quantitatively.

TABLE 2. RELATIONSHIP BETWEEN THE AMPLITUDE OF M1 RESPONSES AND THE GRADE OF SPASTIC TONE*

		Grade of spastic tone				
Stimulus		*1*	*2*	*3*	r_s	*Probability*
20% contraction		(n = 11)	(n = 10)	(n = 2)		
Stretch	100 deg·s^{-1}	1.17 ± 0.10	1.78 ± 0.30	5.73 ± 0.87	0.50	0.015
	200 deg·s^{-1}	1.66 ± 0.09	2.83 ± 0.23	4.41 ± 0.32	0.84	0.00001
Vibration	0.7 mm	1.38 ± 0.23	1.80 ± 0.30	1.81 ± 0.06	0.33	0.14
	1.0 mm	1.57 ± 0.23	2.45 ± 0.32	2.66 ± 0.55	0.45	0.034
'Relaxed'		(n = 4)	(n = 4)	(n = 2)		
Stretch	300 deg s^{-1}	19.75 ± 3.75	36.75 ± 4.63	40.50 ± 8.50	0.77	0.01
Vibration	0.7 mm	28.75 ± 4.77	33.50 ± 6.61	45.50 ± 7.50	0.60	0.07

* Mean values (± SEM) of normalized M1 responses r_s = Spearman rank correlation coefficient. Stretches applied to the voluntarily contracting muscle were 'ramp and hold' and to the 'relaxed' muscle were triangles. Normalization of responses of the 'relaxed' muscle in relation to background levels was possible because all patients showed some slight amount of contraction (< 2% maximum) when attempting to relax fully.

Relation of Reflex Responses to Spastic Tone

The associations between the clinically assessed grade of spastic tone of individual patients and the amplitudes of their short and long-latency reflexes were analysed to determine whether any alteration in reflex activity could reasonably be suggested to underlie abnormal tone.

Table 2 presents the mean values of normalized M1 responses elicited by 'stretch' and vibration in the voluntarily contracting and 'relaxed' muscles of spastic patients who have been subdivided according to their grade of spasticity and indicates the levels of significance of correlations between reflex amplitudes and severity of increased tone. For both the speeds of stretch and the larger amplitude of vibration applied to the contracting muscle and for stretch of the 'relaxed' muscle, such correlations were statistically significant at the 5% level (Spearman rank correlation coefficient). However, although such correlations were present for the group when considered collectively, there was considerable intersubject variability and many exceptions to this overall relationship. Patients with similar clinical degrees of spasticity could have differing reflex amplitudes and conversely patients with comparable sizes of reflex response could have different grades of tone. In addition to such diversity being evident in the sample as a whole, pronounced interpatient variability occurred within each of the main subgroups formed by categorizing individuals according to the neurological disease (MS, ALS) or anatomical lesion (e.g., cord) responsible for their spasticity. Thus despite the significant correlations of M1 amplitude and grade of spasticity demonstrated statistically, the reflex responses measured in the present study cannot be seen to provide the whole answer.

There was no correlation between long-latency stretch responses and the grade of spasticity.

DISCUSSION

The principal new finding of the present study is that vibration of the tendon of flexor carpi radialis evoked an exaggerated short-latency response in patients with spasticity of the upper extremity. A complementary observation, and one crucial to understanding the mechanism of the long-latency stretch response, is that, despite the vibration being maintained for a period comparable to that of the 'stretch' stimulus, the vibration reflex lacked any sign of an M2 component like that elicited invariably by stretch in the normal muscle and usually present, albeit in diminished form, in the spastic muscle.

Previous investigations of the reflex effects of vibration of spastic muscles have been largely confined to abnormalities of the tonic vibration reflex in upper motor neuron disorders. In these studies (e.g., Hagbarth and Eklund, 1968; Burke *et al.*, 1972) uncertainties about the timing of application and of the inertia of the hand-held vibrator precluded accurate latency measurements. Indeed, recognizing these limitations, the workers concerned did not analyse those response components (occurring with 100 ms of stimulus onset) upon which the current work focuses. In keeping with the present observations, however, it was noted that the tonic vibration reflex of spastic patients, as recorded isometrically, developed unusually abruptly and that the accompanying EMG trace often showed an initial phasic burst followed by a protracted silent period.

The early vibration-evoked EMG response which we have described seems certain to have resulted from muscle spindle Gp Ia reflex action. Vibration is known to be a powerful stimulus for human spindle primaries (Burke *et al.*, 1976*a*). Additionally, their latency is comparable to that of H-reflexes (Day *et al.*, 1984) and tendon jerks (Lee and Tatton, 1982) in the same muscle, both of which reflexes are widely held to arise predominantly from Gp Ia influences. Thus the accentuation of vibration reflexes in spasticity may be securely attributed to an enhancement of Gp Ia reflex action in this motor disorder. Such an alteration in Gp Ia reflex action fits well with our parallel observations on short-latency stretch reflexes in spastic muscles which were of increased amplitude and of high velocity sensitivity. These observations extend and complement previously well documented findings of enhancement of H-reflexes (e.g., Olsen and Diamantopoulos, 1967), tendon jerks, short-latency stretch reflex amplitudes (e.g., Lee and Tatton, 1978) and velocity-dependency (e.g., Ashby and Burke, 1971). Thus the present findings fortify the general conclusion that Gp Ia mediated reflexes are enhanced in spasticity.

Mechanism of Enhancement of Gp Ia Action

The short-latency Gp Ia-mediated hyperreflexia of the spastic patients, observed in the present study, cannot be explained simply by abnormally high 'excitability' of the α-motoneurons themselves; if so increased reflexes should generally be paralleled by high levels of background EMG activity. Instead, both vibration and stretch regularly elicited well-developed short-latency responses in the 'relaxed' muscles of the spastic patients but not in those of normal subjects. Additionally, such responses of spastic patients showed relatively small further increases in magnitude, compared with those of normal subjects, when superimposed on voluntary contractions generating background levels of EMG comparable to those found in normal subjects.

Our findings also argue indirectly against the exaggerated short-latency responses of spastic patients having resulted from an especially pronounced Gp Ia afferent volley, due to increased spindle sensitivity (Granit, 1955) or reduced, stimulus-induced, presynaptic inhibition (Delwaide, 1973; Ashby and Verrier, 1976; Iles and Roberts, 1983), impinging upon motoneurons. The small amplitude of the phasic responses of 'relaxed' muscles of normal subjects, evoked by vibration, which is likely to produce a vigorous and synchronous Gp Ia discharge even at rest (Burke *et al.*, 1976*a*), compared with that recorded in spasticity, for which the (so far) limited direct recordings from Gp Ia afferents in spasticity indicate normal levels of spindle sensitivity (Hagbarth *et al.*, 1973, 1975; but *see* Szumski *et al.*, 1974) suggests increased central responsiveness in the clinical disorder. Equally, altered vibration-induced presynaptic inhibition is unlikely to have been a major contributory factor to the short-latency spastic hyperreflexia seen with this form of stimulation. First, such presynaptic inhibition is slow to build up (Somerville and Ashby, 1978); secondly, vibration trains were routinely intermittent and well spaced; and, thirdly, in control experiments shortening the stimulus period to three cycles of vibration produced little detectable effect on the sizes of short-latency responses in either normal or spastic subjects.

Long-latency Stretch Reflexes: Mechanisms of Depression in Spasticity

Compared with the normal, the long-latency (M2) stretch reflexes of spastic patients, in contrast to the exaggeration of preceding short-latency components, were commonly depressed or occasionally absent. Our present observation that response patterns in which M2 components were small or absent were often ones in which M1 peaks were especially large, as has been noted by others (Berardelli *et al.*, 1983; Verrier *et al.*, 1984), suggests that associated increased motoneuronal refractoriness and Renshaw inhibition may have limited later overt activity. However, when the whole population was considered, with spastic and normal data combined (or spastic alone), while a weak trend existed for M1 and M2 responses to vary inversely, the negative correlation was never statistically significant and individual exceptions were found over a wide range of M1 sizes. Thus while motoneuronal refractoriness undoubtedly contributes to depression of M2 responses in spasticity it is unlikely to be solely responsible.

Depression of M2 responses in spasticity may additionally involve enhancement of some active inhibitory mechanism. As argued by Cody *et al.* (1984, 1986), prolongation of M2 responses seen in parkinsonism seems to involve more than just increased efficacy of excitatory inputs and suggests a complementary reduction in counteracting active inhibitory processes. As a corollary, the short duration (as well as smaller amplitude) of M2 responses of spastic patients, particularly evident for more rapid stretches, may well result from an enhancement of such active inhibitory influences.

In control experiments, testing motoneuronal 'excitability' by application of a brief tap (equivalent in size and duration to one vibration cycle) to the tendon at varying delays after the onset of stretch, indicated that recovery occurs earlier during the M1-M2 response complex following relatively slow (100 deg·s^{-1}) than faster (200 deg·s^{-1}, 300 deg·s^{-1}) stretches. However, since both refractoriness and active inhibitory influences (e.g., autogenetic inhibition) would be less potent following slower stretches, this approach, while showing that a second afferent volley is capable of exciting alpha motoneurons at the time at which the late EMG response occurs in normal subjects, does not distinguish between these two as causal factors in the depression of M2 responses in spasticity.

Others have proposed that the reductions of long-latency stretch responses observed in upper motor neuron disorders result from disruption of 'transcortical' pathways (Lee and Tatton, 1975; Marsden *et al.*, 1977; Verrier *et al.*, 1984). However, our new findings of differing responses with stretch and vibration bring a new dimension to the debate. In contrast to stretch, vibration conspicuously failed to elicit EMG responses over the M2 interval in normal or spastic subjects despite being maintained for a similar period to stretch and thus expected to sustain a strongly elevated Gp Ia barrage. We interpret this evidence as indicating that the long-latency stretch reflexes of the normal flexor carpi radialis depend not upon Gp Ia activity but rather upon that of Gp II afferents. A more complete case has been made for the normal flexor pollicis longus (Matthews, 1984*a*, *b*), including the effects on termination of the stimulus. If the general case for Gp II afferents in the genesis of long-latency reflexes is accepted, then it follows that depression of M2 responses, such as was observed in our spastic subjects, could derive from a reduction in Gp II reflex action. Such an alteration in Gp II action could easily result from changes in the 'set' of segmental interneuronal circuits deprived of their normal supraspinal control by lesions of the corticospinal or other descending pathways (Baldiserra *et al.*, 1981).

Overall, we view our present analysis of reflex mechanisms of the wrist flexor muscles, using stretch and vibration, as indicating that the abnormal responses of spasticity arise largely from a reciprocal switching of spinal interneuronal circuits to increase Gp Ia and decrease Gp II spindle excitatory actions. A somewhat similar mechanism has recently been advanced to explain the disordered patterns of EMG responses recorded from leg muscles of spastic patients during stumbling reactions induced by perturbations of gait (Berger, Dietz and Quintern, 1984; Berger, Horstmann and Dietz, 1984). These workers found that early 'monosynaptic' reflexes were exaggerated whereas later responses, which they attributed in normal subjects to 'polysynaptic' Gp II and Gp III spinal reflex action, were reduced or absent.

Relation of Reflex Responses to Spasticity

Finally, the matter arises as to whether the abnormal stretch and vibration reflex patterns that we have studied bear any relation to the mechanisms responsible for spastic tone, especially since spasticity seems to depend critically upon muscle afferent input (*see* Introduction). A suggestive finding for the whole population of patients was of statistically significant correlations between amplitudes of short-latency responses, evoked either by stretch or vibration in contracting and 'relaxed' muscles, and the degree of clinically increased tone. Thus at first sight it is tempting to attribute spastic tone to enhancement of short-latency reflexes. However, individual patients departed from this general picture and there were a number of cases with clinically similar tone despite varying M1 sizes. This was equally true for the sample when considered as a whole or divided into subgroups, themselves inevitably heterogeneous, according to the aetiology (MS, ALS, cord lesions) of their spasticity. Similarly, there was considerable interpatient variability in the relationship between the amplitudes of tendon jerks and the severity of spasticity, as previously reported for these muscles (Lee *et al.*, 1983). Therefore spasticity at the wrist cannot be uniquely ascribed to short-latency hyperreflexia. A related observation is that the exaggerated 'monosynaptic' EMG responses of calf muscles of spastic patients which occur during walking appear to contribute little to net tension measured at the Achilles tendon (Berger, Horstmann and Dietz, 1984). Nothing can be said of long-latency responses other than that, in our patients, they were on average reduced and appear incapable of having produced any appreciable resistance to movement. Thus the question remains unsolved and, in common with other recent workers (e.g., Berardelli *et al*, 1983; Lee *et al.*, 1983), we are forced, noting the variability of EMG patterns, to conclude that there may be several factors contributing to the development of spastic tone and that the mechanisms involved may vary according to the exact nature of the causative lesion.

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LOCALIZATION, TIMING AND SPECIFICITY OF GATING OF SOMATOSENSORY EVOKED POTENTIALS DURING ACTIVE MOVEMENT IN MAN

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SUMMARY

Short latency somatosensory evoked potentials (SEPs) to median nerve stimulation were recorded at different times simultaneously and after an order to move the ipsilateral thumb (0, 100, 200, 300, 400 and 780 ms). Brain potentials were derived from surface electrodes over the scalp at contralateral postcentral and precentral sites and muscle potentials were derived from surface electrodes over the thenar eminence. Ipsilateral thumb movement did not affect the early lemniscal P14 or the postcentral cortical N20 but was accompanied by attenuation of the cortical postcentral P27 and cortical precentral P22, N30 and P45. These results suggest that the gating induced by voluntary movement in man occurs at thalamocortical level and that the differential effect on postcentral N20 and precentral P22 may represent the activity of different generators.

Gating of SEPs during voluntary movement begins approximately 80–100 ms *before EMG onset*, is maximal at the time the EMG is maximal, and returns to control values after the EMG is concluded. These results suggest that the gating that precedes the onset of EMG activity is related to premotor events in the cerebral cortex and not to centripetal influences. Gating of SEPs to median nerve stimulation was localized to movements of areas innervated by the median nerve, that is, the ipsilateral thumb, index or middle finger, but not to movements of ipsilateral little finger or contralateral thumb.

INTRODUCTION

Several studies have shown an attenuation of somatosensory input to the cerebral cortex during voluntary movement (Coquery *et al.*, 1972; Lee and White, 1974; Papakostopoulos *et al.*, 1975; Jones, 1981; Rushton *et al.*, 1981). This phenomenon, termed gating, has been discussed with respect to its possible central or peripheral origins (Ghez and Pisa, 1972; Coulter, 1974; Rushton *et al.*, 1981; Angel *et al.*, 1984). Animal experiments suggest that the locus of this gating is within the central nervous system (CNS) at subcortical sites (Coquery *et al.*, 1972; Ghez and Pisa, 1972; Coulter, 1974), but the site of gating of human afferent somatosensory volleys during voluntary movement is not known.

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There are several electrophysiological events that occur in the cerebral cortex before the initiation of a voluntary movement. The contingent negative variation (CNV) appears during the period between a warning signal and the subsequent order to move (Walter *et al.*, 1964; Tecce, 1972). The Bereitschaftspotential is a slow negative wave occurring within one second before self-paced movements (Kornhuber and Deecke, 1965; Vaughan *et al.*, 1968; Shibasaki *et al.*, 1980). Finally, there is an increase in the firing rate of neurons in the motor cortex during the preparatory and precontraction periods of the movement (Schmidt *et al.*, 1974; Tanji and Evarts, 1976; Kubota and Hamada, 1979). The occurrence of these electrophysiological events suggest the possibility that gating of somatosensory input is initiated before the onset of movement as occurs in the visual system when visual thresholds are affected prior to the initiation of saccades (Latour, 1962; Zuber and Stark, 1966; Starr *et al.*, 1969). Contradictory results were reported in two papers regarding the modification of somatosensory afferent volleys prior to movement in humans. Coquery *et al.* (1972) found an increase in somatosensory evoked potentials (SEPs) before movement while Hazemann *et al.* (1975) reported a significant attenuation of SEPs beginning 440 ms before a voluntary movement. The results to be presented in this paper show that gating of somatosensory input in humans occurs *before* the initiation of a voluntary movement with its locus of action occurring in the CNS at thalamic and/or cortical levels. Moreover, the gating of sensory input is particular for movements of portions of the body from which the somatosensory input originates.

METHODS

Subjects

Recordings were obtained from 10 healthy subjects (5 men and 5 women), aged 15 to 32 years They were tested in a sound attenuating chamber while seated comfortably. The left hand and forearm were attached comfortably to the arm of the chair allowing free movement of the fingers.

Stimulation Procedures

Percutaneous electric stimulation with bipolar electrodes was delivered to the left median nerve at the wrist. The intensity of the stimuli was adjusted to elicit a just visible twitch of the thenar muscles without causing pain. The number of stimuli delivered during control and movement condition was that necessary to evoke short latency somatosensory cerebral components ($<$ 50 ms) resulting in a 20% or less amplitude difference on repeated control measures in the same subject and at the same session. This varied among subjects from 400 to 1400 stimuli depending on the relationship of the evoked potentials to the background EEG, etc. (i.e., signal/noise ratio). Clicks were presented through earphones as the order to move. The clicks were generated by passing 100 μs duration pulses through the earphones at an intensity that was low (from 10 to 25 dB SL) but still clearly detectable.

Recording Procedures

SEPs were recorded with surface electrodes placed unilaterally or bilaterally at all or some of the following positions (fig. 1): (1) a postcentral electrode 3 cm behind the vertex Cz and 7 cm from the midline; (2) a precentral electrode 2 cm in front of Cz and 5 cm from the midline; (3) a frontal electrode 7 cm in front of Cz and 5 cm from the midline; and (4) a prefrontal electrode 9 cm in front of Cz and

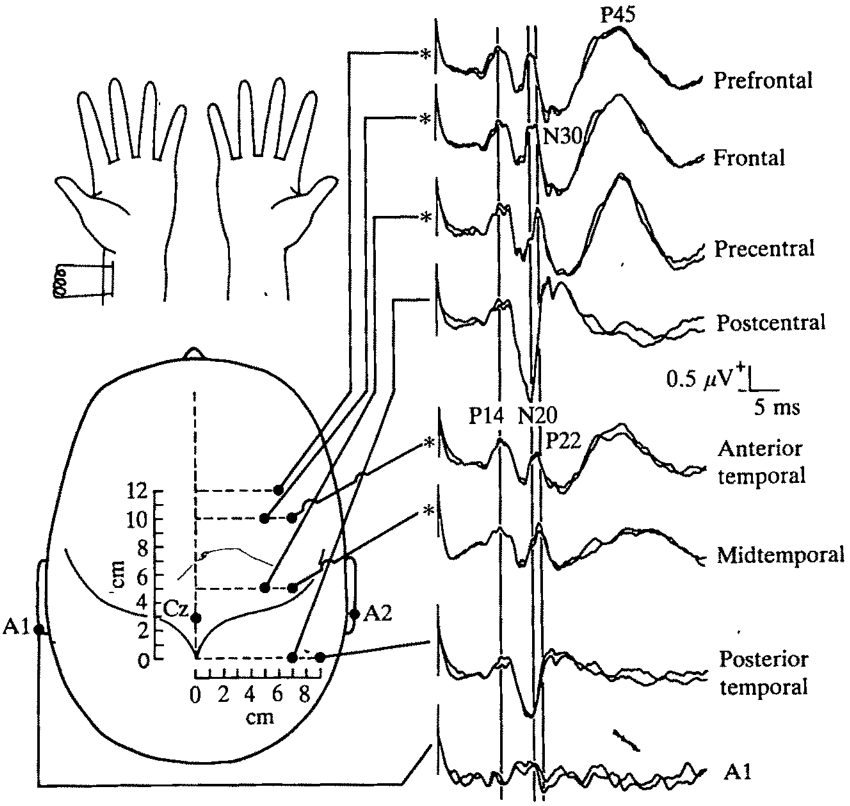

FIG. 1 Scalp distribution of left median nerve SEPs. The components are labelled by their polarity and their approximate latencies (P14, N20, P22, N30 and P45). Vertical lines have been placed at the peaks of the subcortical P14, postcentral N20 and precentral P22 components The scale over the scalp refers to the interelectrode distances. An asterisk (*) is placed before the averages obtained from precentral recording sites. Reference electrode at A2

6 cm from the midline. Additional electrodes were placed 2 cm lateral to postcentral, precentral and frontal locations. In every case the reference was the earlobe ipsilateral to the recording electrodes, chosen to differentiate more effectively the postcentral and precentral components of median nerve SEP (N20 and P22) (Desmedt and Cheron, 1981; Mauguière *et al.*, 1983).

Electrode impedances were below 5 kΩ. The potentials were amplified with a gain of 500,000 using a bandpass of 30–3000 Hz (6 dB/octave slope) and averaged over a 51 ms time period with a dwell time of 0.1 ms and 512 points per channel. The EMG was recorded by a pair of surface electrodes placed over the thenar muscles and the resulting activity amplified and full wave rectified. EMG onset was signalled by a Schmitt trigger that was capable of triggering the averager when so desired. Movement related evoked potentials accompanying thumb movement were recorded by backaveraging the EEG (bandpass of 0.1–3000 Hz) time-locked with the EMG onset.

In 3 subjects we recorded simultaneously EEG activity at bilateral postcentral and precentral locations, EMG activity from the thenar eminence, and trigger signals from the clicks (order to move) and electric pulses (median nerve stimulation) on magnetic tape. Off-line analysis allowed us to analyse the trial by trial latencies of EMG from the thenar eminence, short-latency SEPs to median nerve stimulation, and movement-related EPs.

Experimental Paradigms

Effects of moving the thumb ipsilateral to median nerve stimulation. Pairs of click-median nerve stimuli separated by 250 ms were regularly delivered at 0.6/s in 10 subjects. They were instructed to respond to the clicks by flexing the thumb as quickly as possible after the click or, as a control, to relax. Control recordings were interspersed with those obtained during the different movement conditions. The interval of 250 ms was chosen to ensure that motor activity was already present when somatosensory stimuli were applied. Consistency of movements along each session was stimulated by the promise of financial reward and ensured by the experimenter's visual control of the behaviour.

Effects of varying time intervals between click and median nerve stimulation. Three of the subjects were also tested when median nerve stimulation was delivered simultaneously with the clicks (0 condition) or at 100, 200, 300, 400 and 780 ms after the clicks to encompass the precontraction, contraction and postcontraction periods. The order in which the intervals were selected was randomized. Subjects were instructed to respond to the clicks by flexing the thumb as in the first condition (Starr and Cohen, 1985).

Effects of moving different fingers. Five subjects were tested with an interval of 250 ms between clicks (order to move) and median nerve stimulation as in the first paradigm. They were instructed to respond to the clicks by flexing thumb, index, middle, little finger or the contralateral thumb. When asked to move the little finger, 3 of the subjects moved the little and ring fingers together.

Data Analysis

Sensory and movement related evoked potentials were analysed off-line. Amplitude and latencies of the various components of the recorded potentials were measured from a computer display with a cursor. SEP latencies to median nerve stimulation were measured from the onset of the electric shocks activating the median nerve. As the peak latencies of the SEP components showed small differences between averages we systematized the measurements of amplitude by choosing the maximal peak within a 5 ms range (±2.5 ms) of the latencies of the control peaks. Absolute amplitudes of the SEP were measured between baseline and positive or negative peaks. Baseline was established by the computer defining the mean value across the entire waveform. This value was then substracted from the peaks and troughs comprising the components The amplitudes of SEPs recorded during movement are expressed as a percentage of controls recorded during the relaxed conditions in the same subject and session. We found that the clicks evoked inconstant evoked potentials because of their low intensity level (10–25 dB SL) and thus the amplitude of median nerve SEPs preceded by clicks did not differ from those without clicks if subjects were not moving.

Movement-related evoked potentials to thumb movement were back averaged from EMG onset obtained from the thenar eminence.

Statistical Analysis

Repeated measures analysis of variance (ANOVA) was used to obtain overall F values for the different groups of control and movement conditions. When justified by a significant overall F ($P < 0.05$), Duncan's multiple range test for nearly equal numbers was used to provide more detailed comparisons between the attenuation of different components of median nerve SEPs, the effects of different finger movement and the different time intervals between clicks and shocks. The relationship between attenuation of median nerve SEPs and time intervals between click and shocks was evaluated by the Pearson r correlation coefficient.

RESULTS

Electric stimulation of the median nerve evoked reproducible cerebral potentials with configurations that differed according to the location of the recording electrodes (fig. 1). A major difference was found between postcentral and precentral electrodes.

At the postcentral sites (postcentral and posterior temporal in fig. 1) there was an initial positive component peaking at 13.5 ± 1.0 ms (P14), followed by negative and positive components at 18.0 ± 1.0 ms (N20) and 23.5 ± 2.7 ms (P27), respectively (Table 1, fig. 1).

TABLE 1. COMPONENTS OF MEDIAN NERVE SEPs*

	Postcentral			*Precentral*			
Subjects	*P14*	*N20*	*P27*	*P14*	*P22*	*N30*	*P45*
1	12.4	18.5	24.5	12.6	19.6	26.0	37.0
2	13.5	19.3	24.0	13.8	20.5	26.2	33.2
3	14.8	18.4	22.0	13.2	19.3	22.3	37.2
4	12.7	17.1	21.2	12.8	18.4	21.4	35.8
5	12.5	18.6	22.0	12.7	18.8	25.0	40.0
6	13.0	19.0	29.1	13.1	20.0	28.9	40.0
7	14.1	17.7	23.2	14.1	18.8	22.6	40.0
8	13.0	17.2	26.8	13.2	18.6	27.7	34.7
9	15.3	18.7	22.0	15.2	20.3	25.2	38.6
10	14.0	16.0	20.0	13.8	18.0	27.4	36.0
Mean	13.5	18.0	23.5	13.4	19.2	25.3	37.2
SD	1.0	1.0	2.7	0.8	0.8	2.5	2.4

* Latencies of cerebral potentials to median nerve stimulation (ms).

The P14, N20 and P27 components were present in each of the 10 subjects tested. After P27 only 4 of the 10 subjects showed subsequent negative and positive components (N, P) which we chose not to include in this study. At the precentral sites (the traces with an asterisk, i.e., prefrontal, frontal, precentral, anterior and middle temporal in fig. 1) the only similarity to the postcentral sites was an initial positive component peaking at 13.4 ± 0.8 ms (P14). The subsequent positive, negative and positive components at 19.2 ± 0.8 ms (P22), 25.3 ± 2.5 ms (N30) and 37.2 ± 2.4 ms (P45), respectively, were particular to the precentral sites (Table 1, fig. 1). The P14, N30 and P45 precentral components were present in each of the 10 subjects tested. However, there was some variability in the P22 in all subjects (very clear in subjects 1, 2, 3, 4, 5, 6, 7 and 10, less well defined in subjects 8 and 9 of fig. 2). The grand average of the 10 subjects also shows a very clear P22 (fig. 2B).

Effects of Thumb Movement on Median Nerve Somatosensory Afferent Volley

Ipsilateral thumb movement substantially diminished the postcentral P27 in all 10 subjects tested to 53.8 ± 20.3% ($P < 0.01$). In contrast, the P14 was variously affected, being smaller in 3 subjects (nos 6, 7, 9) and larger in 5 (2, 3, 4, 8, 10). The N20 was also variously affected, being smaller in 4 (2, 5, 6, 8) and larger in 3 (1, 9, 10). Thus the grand average of the P14 and N20 components showed no change with

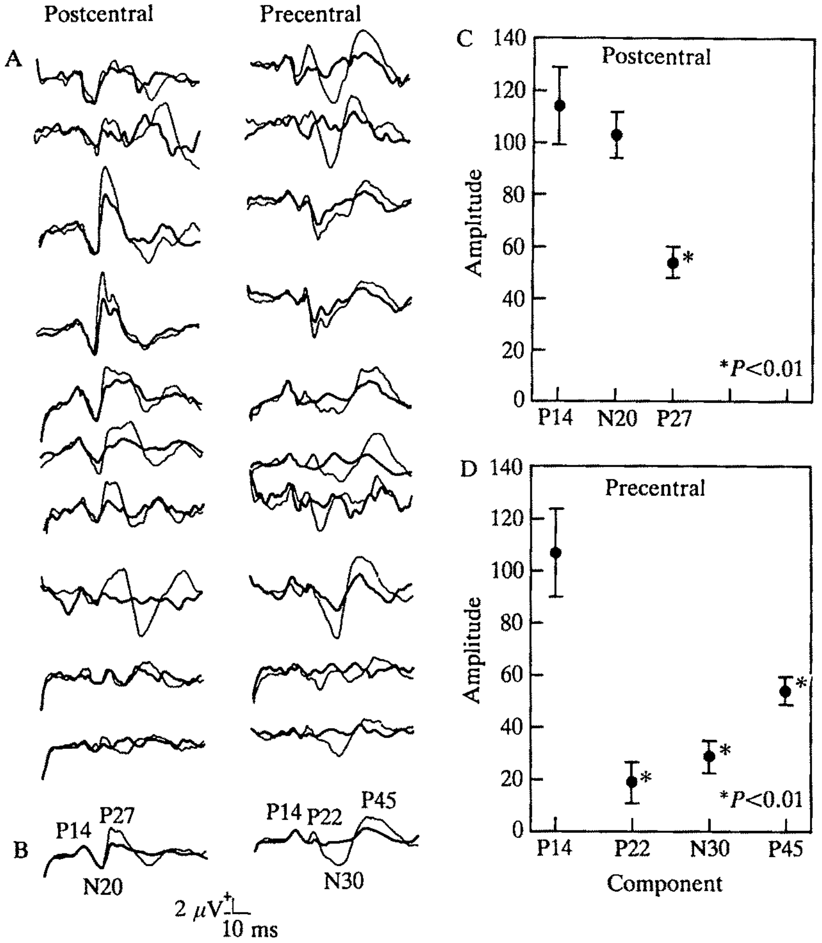

FIG. 2. Effects of thumb movement on ipsilateral median nerve SEPs at postcentral and precentral positions. A, individual averages of the 10 subjects; B, grand average of these 10 subjects In this and all subsequent figures the thin lines represent the control averages while the thick lines represent the averages obtained during movement. The amplitude changes of the different components accompanying movement are plotted in C for the postcentral site and D for the precentral site. Amplitude values are expressed as percentages of each component compared with control values (means ± SEM). In the text, reference is made to each subject by numbering in sequence from the topmost trace. Reference electrode on ipsilateral earlobe.

movement (114.0 ± 49.0% and 103.2 ± 29.0%, respectively, n.s.) (*see* Table 2 and bottom row of traces in fig. 2).

Thumb movement was also associated with a reduction in the precentral P22, N30 and P45 in the 10 subjects tested (to 19.5 ± 26.3%, 29.0 ± 18.9% and 53.8 ± 18.1%, respectively, $P < 0.01$) while the P14 was variously affected with the grand average showing no change (107.0 ± 55.4%, n.s.) (*see* Table 2 and fig. 2). The attenuation observed in contralateral postcentral P27 and precentral P22, N30 and P45 was also significant when compared with the amplitudes of the postcentral and precentral

P14 ($P < 0.01$ for all components). The peripheral afferent input was unchanged during the different experimental conditions. This is supported by the lack of changes in subcortical P14 and cortical N20 in the postcentral position and P14 in the precentral position. Moreover, in subsequent experiments (Tapia *et al.*, 1985, 1986), we also measured the amplitude of peripheral nerve evoked potentials at Erb's point and these also did not change during movement compared with control conditions. The effects of movement on attenuating median nerve somatosensory evoked potentials were not limited to the contralateral scalp since the precentral N30 was also attenuated in the precentral area *ipsilateral* to the limb being moved in the 3 subjects tested (*see* fig. 3).

TABLE 2 EFFECTS OF THUMB MOVEMENT ON THE AMPLITUDE OF SEPs*

	Postcentral			*Precentral*			
Subjects	*P14*	*N20*	*P27*	*P14*	*P22*	*N30*	*P45*
1	100	150	61	250	4	27	47
2	132	88	69	100	14	17	83
3	150	100	59	117	27	64	50
4	150	102	58	65	43	61	61
5	103	86	64	104	0**	18	54
6	86	67	43	115	0**	6	32
7	70	100	38	102	26	25	83
8	200	72	31	101	81	29	44
9	24	112	92	44	0**	26	30
10	125	155	23	72	0**	17	54
Mean	114.0	103.2	53.8	107.0	19.5	29.0	53.8
SD	49.0	29.0	20.3	55.4	26.3	18.9	18.1
P	n.s.	n.s.	< 0.01	n.s.	< 0.01	< 0.01	< 0.01

* Amplitudes of cerebral potentials to median nerve stimulation expressed as percentage of control values (100%). ** The component could not be distinguished from baseline. n.s. = not significant.

We attempted to assess the physiological significance of the attenuation accompanying movement by relating it to the change in amplitude of SEP with changes in stimulus intensity. The extent of the attenuation of the SEP components that accompanied movement (between 30 and 60%) is equivalent to the attenuation that accompanies a decrease in the intensity of median nerve stimulation from one third to two thirds of the motor threshold. However, such a decrease in stimulus intensity was accompanied by attenuation of *all* subcortical and cortical components, whereas attenuation during movement was component-specific (*compare* figs 2 and 4).

To control for the effects of the regularity of stimulus presentations on reaction times and SEP changes we tested 2 subjects at both the regular rate of 0.6/s and at an irregular rate of approximately 0.3/s. This allowed us to analyse the EMG onset on a trial by trial basis and define the contribution of anticipation in regular versus irregular presentations since such differences in stimulus rate, per se, do not modify reaction times greatly (Klemmer, 1967; Niemi and Näätänen, 1981). EMG onset occurred on the average 62.5 ms earlier for regular presentations (latencies in the

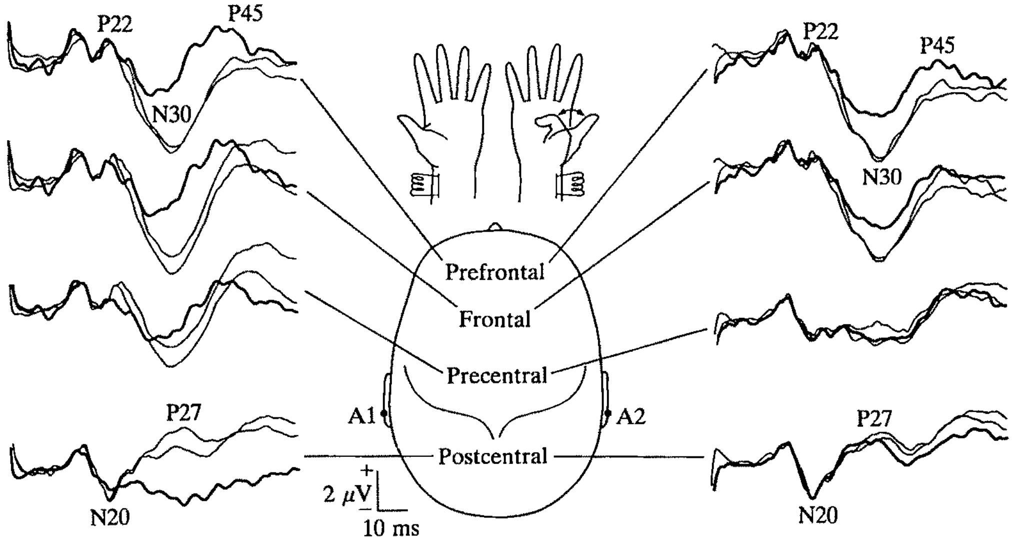

Fig. 3. Effects of right thumb movement on SEPs to bilateral median nerve stimulation at the wrist. Note that N20 and P27 and P22 and P45 are attenuated only over the left scalp, whereas N30 is attenuated bilaterally. The P14 is also unaffected bilaterally. Reference electrode on ipsilateral earlobe.

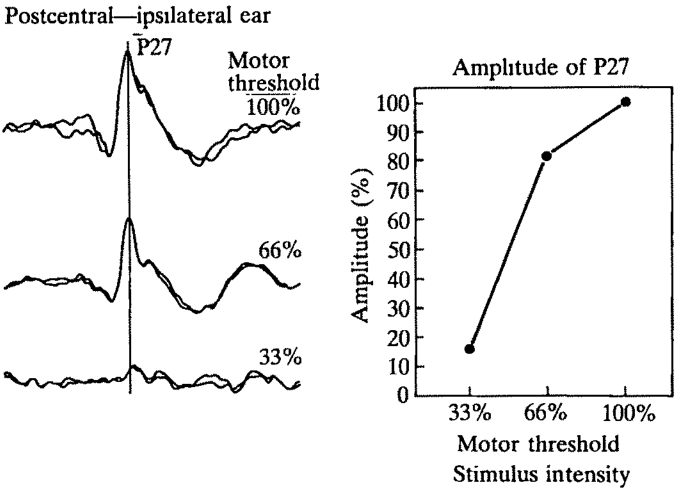

Fig. 4. Effects of median nerve stimulus intensity on the amplitude of the postcentral P27. The stimulus necessary to evoke a slight thenar twitch in this subject was 9 mA (100%); 3 mA (33%) represented the sensory threshold, and 6 mA (66%) was twice sensory threshold.

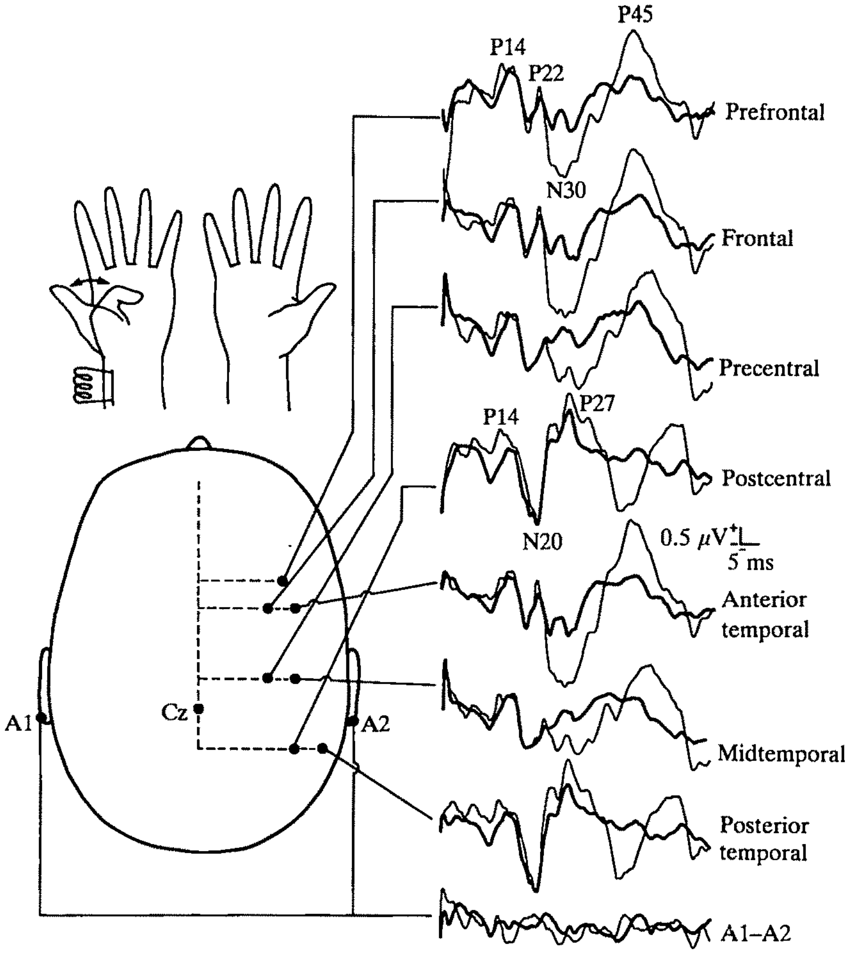

FIG. 5. Scalp distribution over the right scalp of the effects of left thumb movement on SEPs to left median nerve stimulation at the wrist. Note that postcentral P27 is slightly attenuated at both postcentral and posterior temporal sites and precentral P22, N30 and P45 are attenuated at prefrontal, frontal, anterior temporal and middle temporal sites. The P14 and N20 are also unaffected.

2 subjects were 213 ± 72 and 144 ± 36 ms) than for irregular presentations (latencies in the 2 subjects were 276 ± 58 and 206 ± 85 ms) but the attenuation of SEP during movement was comparable at the two presentation rates. The variability of the reaction times observed in these experiments might be a factor in 'smoothing' the curves of amplitude attenuations as a function of the click-shock intervals.

The scalp distribution of the median nerve SEPs during control and movement conditions is shown in fig. 5 in 1 subject. Postcentral P27 and precentral P22, N30 and P45 were attenuated at the different electrode sites while the P14 and N20 were not affected. The latencies of the different components of the median nerve SEPs did not change during these experiments.

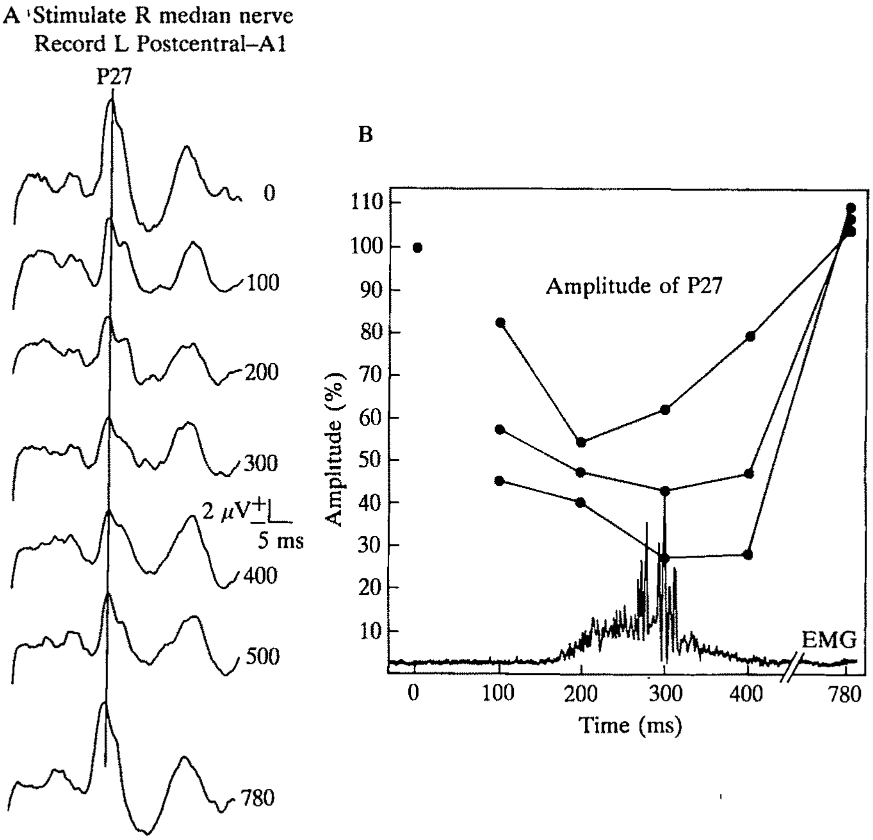

FIG 6. Effects on SEPs of stimulating median nerve simultaneously and at different times after the command to move the thumb for 3 subjects. The abscissa refers to the time interval in ms between the command to move (the click) and the shock to the median nerve. The evoked potentials from one of the subjects is shown in A and the amplitudes of P27 from the 3 subjects are shown in B. The time course of the rectified EMG from 1 subject is shown at the bottom of B with the EMG onset adjusted to the mean latency of EMG onset in the 3 subjects Note that P27 is attenuated at 100 ms, before the occurrence of muscle activity, and remained attenuated until 400 ms, returning to control values at 780 ms when EMG activity was completed.

These results indicate that the effects of thumb movement on diminishing the amplitude of median nerve sensory volleys recorded over the scalp occur central to the generation of P14 and N20.

Effects of Varying Time Intervals between Click and Shocks

In 3 subjects, median nerve stimulation was delivered at 100, 200, 300, 400 and 780 ms after the clicks. The results are depicted graphically together with one of the subject's evoked potentials and rectified EMG in fig. 6. There was an attenuation of the P27 component *before* the initiation of the EMG. At a latency of 100 ms after the command to move (click) during the precontraction period the P27 diminished to $61.3 \pm 19.2\%$ ($P < 0.01$). At 200, 300 and 400 ms, during the contraction period, the

P27 component diminished to 47.3 ± 7.0% ($P < 0.01$), 44.0 ± 17.1% ($P < 0.01$) and to 52.3 ± 25.8% ($P < 0.01$), respectively. Finally, at 780 ms during the postcontraction period the P27 component returned to control values to 107.5 ± 2.5% (n.s.).

Movement-related Potentials

In an attempt to differentiate the median nerve SEPs from thumb movement-related evoked potentials we back averaged from EMG onset and recorded from F3 and P3 referenced to the ipsilateral ear when only the command to move (the click) was presented without an associated median nerve stimulus. We were unable to define a consistent movement-related evoked potential using this montage and paradigm making it unlikely that the algebraic summation of such movement-related potentials with the SEPs were responsible for the SEP amplitude attenuation.

TABLE 3 EFFECTS OF THE MOVEMENT OF DIFFERENT FINGERS ON SEPs*

	Ipsilateral				*Contralateral*
Subjects	*Thumb*	*Index*	*Middle*	*Little*	*Thumb*
1	37	50	91	64	82
2	94	55	55	76	132
3	12	5	12	48	90
4	68	21	66	103	95
5	16	52	24	72	80
Mean	45.4	36.6	49.6	72.6	95.8
SD	35.1	22.3	31.9	20.1	21.1
P	< 0.01	< 0.01	< 0.01	n.s.	n.s.

* Amplitudes of cerebral potentials to median nerve stimulation expressed as percentage of control values (100%).

Effects of Moving Different Fingers

The attenuation of median nerve somatosensory afferent input that accompanied movement was localized to the hand stimulated. In 5 subjects the postcentral component P27 diminished to 45.4 ± 35.1% ($P < 0.01$) during ipsilateral thumb movement but was not affected by movements of the contralateral thumb (95.8 ± 21.1%, n.s.) (fig. 3). Moreover, the attenuation of P27 was not similar for all ipsilateral finger movements. P27 diminished to 36.6 ± 22.3% ($P < 0.01$) during ipsilateral index finger movement, to 49.6 ± 31.9% ($P < 0.01$) during ipsilateral middle finger movement and to 72.6 ± 20.1% (n.s.) during ipsilateral little finger movement (fig. 7, Table 3).

In 1 subject we stimulated simultaneously both median nerves and recorded bilaterally (fig. 3) while the subject was moving the right thumb. The attenuation of postcentral N20 and P27 and precentral P22 is clearly localized to the hemisphere contralateral to the hand being moved, whereas N30 in precentral sites was

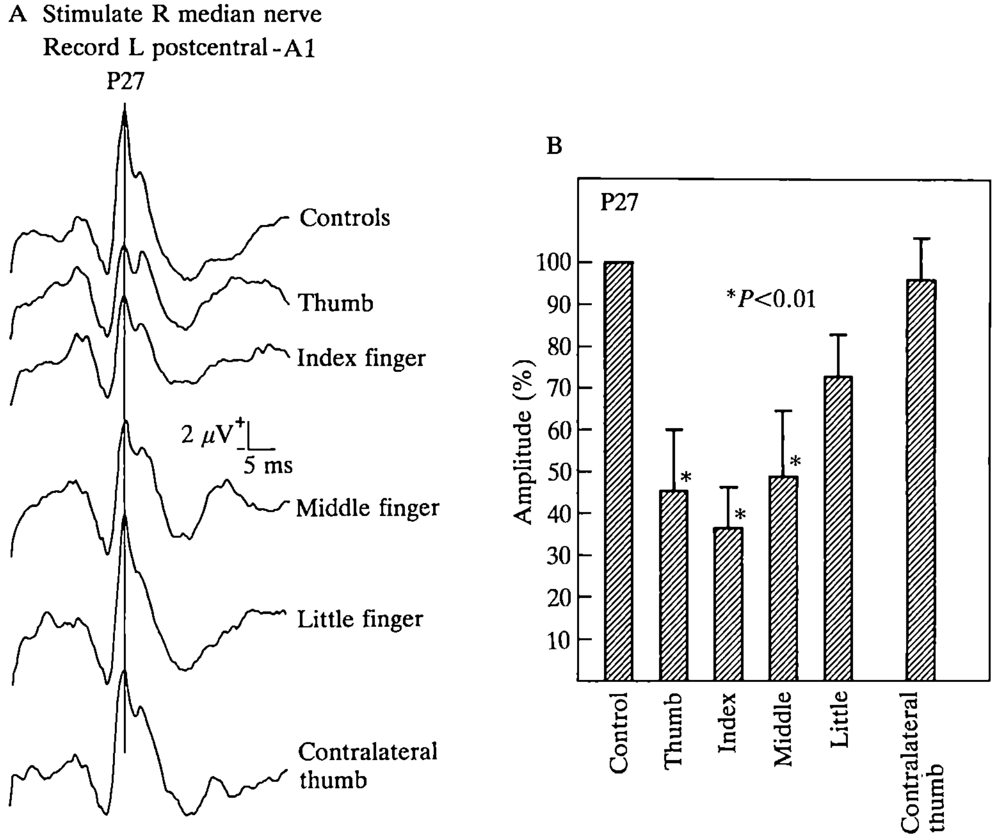

FIG. 7. Effects of moving different digits on median nerve SEPs. Results from a representative subject are shown in A and the mean of the amplitude (+SEM) of P27 in 5 subjects in B. Note that attenuation of P27 occurred during movement of those digits innervated by the stimulated median nerve (i.e., thumb, index and middle fingers) whereas contralateral thumb or ipsilateral little finger movements were without effect.

attenuated bilaterally during this task. These experiments showed that the gating of afferent somatosensory input arising from stimulation of the median nerve accompanied movements of those structures innervated by that nerve.

DISCUSSION

Locus of the Gating

The results of this study in humans using scalp recording techniques show that gating of somatosensory input evoked by stimulating the median nerve occurs central to the generation of the scalp derived P14 and N20 components. P14 is preserved in patients with thalamic lesions (Mauguière and Courjon, 1981) and most probably originates from the medial lemniscus with its onset corresponding to activation of caudal lemniscal fibres and its peak representing arrival of the lemniscal signal at the thalamus (Desmedt and Cheron, 1981). The subcortical P14 component was recorded at several different electrode positions and did not change during thumb movement, showing no evidence for gating of somatosensory input below cortical level. We also know from other control studies that the peripheral nerve volley recorded over Erb's point was also unaffected by the movement (Tapia, Cohen and Starr, unpublished observations). The postcentral N20 was unchanged during thumb movement whereas the precentral P22 was attenuated. Since N20 is generated most probably in the primary somatosensory cortex (Emerson and Pedley, 1984) while P22 is generated in the frontal cortex (Desmedt and Cheron, 1981; Mauguière *et al.*, 1983), there is a differential gating effect of movement on cortical somatosensory processes. We have considered two explanations to account for this phenomenon. (1) N20 and P22 may be generated by separate thalamocortical pathways to parietal and frontal lobes, respectively, as proposed by Desmedt and Cheron (1981) and Papakostopoulos and Crow (1984). A gating of the P22 component could occur at thalamic or cortical level without affecting the separate thalamocortical pathway responsible for N20 (Asanuma, 1981; Evarts, 1981; Jones, 1983). The subsequent attenuation of the postcentral P27 could result from corticocortical inhibitory connections. (2) Alternatively, P22 may be generated serially after N20 through corticocortical connections between parietal areas 2 and 5 and frontal areas 4 and 6 (Asanuma, 1981). If this were the case, gating would occur in the cerebral cortex somewhere between the generators of N20 and P22 but affecting selectively P22. In patients with lesions in the postcentral cortex, changes in N20 occur without modification of P22, giving less credance to this last possibility (Mauguière *et al.*, 1983).

If the locus of the gating involves the cerebral cortex as our results strongly suggest, two mechanisms may be responsible for the attenuation of SEPs. (1) Cortical motor neurons involved in thumb movement also take part in the generation of the cortical SEPs. Thus during movement, those neurons controlling thumb movement are unable to react to median nerve stimulation, resulting in a smaller amplitude SEP. This mechanism could also account for the selective attenuation of the precentral P22 which reflects activity of motor neurons without influencing the postcentral N20 originating from sensory neurons. (2) Cortical motor neurons involved in producing the requested movement might suppress other cortical neurons involved in the generation of the SEP, a form of corticocortical inhibition (Porter, 1981).

Timing of the Gating

The gating of somatosensory evoked potentials associated with movement begins before the initiation of EMG activity. In agreement with these results, sensory thresholds are elevated *before and during* voluntary movement in the stimulated limb (Papakostopoulos *et al.*, 1975; Coquery, 1978; Angel *et al.*, 1984).

There are several indices of cerebral cortical activity that *precede* movement. (1) The movement related potentials evoked by self-paced thumb movements (MP) show changes in the cerebral cortex before the initiation of the movement. The MP is composed at least of three main components: a slow negative shift (Bereitschaftpotential) appearing 1 s before EMG onset, a positive-negative deflection between 50–150 ms before EMG onset and, finally, a positive deflection between 50–150 ms after EMG onset (Gilden *et al.*, 1966; Shibasaki *et al.*, 1980). The sequence of the three electrophysiological findings has been related physiologically to the facilitation of the motor cortex, activation of pyramidal tract and kinaesthetic feedback respectively (Schmidt *et al.*, 1974). (2) Approximately 12% of task-related cortical neurons in the motor cortex increase their discharge frequency at least 250 ms before EMG onset with the majority of the task-related neurons changing discharge rate between 50–150 ms before EMG onset (Schmidt *et al.*, 1974). Recall that it is in this same time period (100 ms) that the gating of SEPs becomes clear. (3) The CNV (contingent negative variation) is a heterogeneous electrical brain wave recorded over the scalp when a preparatory stimulus (S1) is followed by an imperative stimulus (S2) to which a motor response is made. It begins approximately 300 ms after S1 and has an abrupt decline about 120 ms after S2. It is bilaterally symmetric (Cant *et al.*, 1966) in contrast to the contralateral topography of movement-related potentials (Vaughan *et al.*, 1968). The CNV is most clearly related to the psychological processes of attention and arousal (Tecce, 1972). Our design did not allow study of events between S1 and S2, but only after S2 (order to move). The CNV amplitude decreases after S2 while the gating of SEP associated with the command to move increases making a relation between CNV and gating unlikely.

We examined the relation between movement-related potentials (MP) and the attenuation of SEPs in the 3 subjects tested for the 'timing' experiments, all of them showing very clear movement-related potentials to 'self-paced' thumb movements. For this purpose we back-averaged from EMG onset and recorded from F3 and P3 referenced to the ipsilateral ear. We were unable to define a consistent movement-related evoked potential by this method making unlikely that such movement-related potentials influenced SEP's amplitudes. The failure to detect such movement-related potentials is troublesome but may represent the fact that the commanded movements occurred at a relatively fast rate (1 per 2 s) whereas during self-paced movements the clearest motor potentials were obtained at relatively slower rates (1 per 5–10 s).

Mechanisms of the Gating

There is some agreement that the *location* of gating during active movement occurs centrally but its mechanism has been unclear. Two hypotheses have been proposed. (1) Efferent impulses from upper motor neurons may be transmitted to sensory relay nuclei and other areas of the cerebral cortex leading to gating of afferent volleys as has been described in animals at the dorsal spinal cord (Fetz, 1968), the dorsal column nuclei (through presynaptic and postsynaptic inhibition) (Ghez and Pisa, 1972) and the thalamus (Tsumoto *et al.*, 1975; Yingling and Skinner, 1977). Our results in humans show a cortical or thalamocortical site for gating (i.e., subcortical P14 is unaffected, while cortical P22, P27, N30 and P45 are attenuated). (2) Ascending afferent volleys generated in the periphery by the movement may be able to interact in the CNS to gate other 'less relevant' inputs (Angel *et al.*, 1984). This phenomenon is possible since somatosensory evoked potentials to stimulation of slowly conducting cutaneous afferents may be suppressed by synchronously elicited activity in IA afferents (Burke *et al.*, 1981). However, during a voluntary contraction the onset of EMG activity precedes the afferent discharge of muscle spindles (Vallbo, 1973), making it unlikely that a centripetal mechanism could account for gating occurring prior to the onset of movement.

Specificity of Gating

The gating of SEPs by voluntary motor activity is well localized. Median nerve SEPs were attenuated by moving those portions of the limb innervated by that nerve, that is, ipsilateral thumb, index or middle finger, but not ipsilateral little finger or contralateral thumb. Perhaps the portions of the motor cortex involved in these median nerve movements innervated become insensitive to input from the median nerve for a period of time both before and during the movement to account for the phenomenon of gating of SEP (Asanuma *et al.*, 1968; Rosén and Asanuma, 1972). The topographical selectivity of SEP attenuation in our experiments points to a very localized process in the gating of afferents to the cerebral cortex.

Gating of sensory input has also been shown to occur in the visual system where saccadic eye movements are associated with changes in discharge patterns in the lateral geniculate body (Malcolm *et al.*, 1970) and cerebral cortex (Adey and Noda, 1973). Moreover, the detection of a test flash diminishes both *before and during* the initiation of a saccade (Latour, 1962; Zuber and Stark, 1966; Starr *et al.*, 1969). The results presented in this paper show that gating in the somatosensory system in man also occurs both before and during motor activity. It may be that 'gating' of different sensory modalities in man have common mechanisms and function.

The interrelation between sensory input and motor activity defined in this study may have relevance for the investigation of clinical disorders of motor function. For instance, it is possible that patients with disturbed motor function due to various structural or neurochemical mechanisms (e.g., Huntington's chorea, Parkinson's disease, pyramidal tract lesions) may have alterations in both the extent and timing of such gating of somatosensory input. The methods and normative results presented in this paper will allow the study of such sensorimotor interactions in patients with neurological disorders.

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THE ROLE OF INSULIN RESISTANCE IN THE PATHOGENESIS OF MYOTONIC MUSCULAR DYSTROPHY

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SUMMARY

A study of glucose, insulin, lipids and lipoproteins in myotonic dystrophy (MyD) has shown elevation of fasting plasma insulin, triglycerides and very low density lipoproteins (VLDL) but no significant difference from normal in the fasting plasma glucose, total cholesterol or low and high density lipoproteins. Elevation of the total triglyceride and VLDL levels showed a direct relationship to hyperinsulinaemia. Insulin binding to cultured MyD fibroblasts under optimal conditions was significantly reduced but there was no difference in receptor affinity between MyD and control cells. In contrast to insulin binding, LDL binding to MyD fibroblasts was normal although there was a tendency to reduced LDL binding at 37° C that may reflect mildly reduced lipid metabolism. The alterations in lipids and insulin in MyD are compatible with insulin resistance. Laboratory and clinical findings in MyD were compared with other inherited insulin-resistant diseases. MyD showed marked similarity to a group of disorders that have mild insulin resistance and mildly elevated plasma insulin in contrast to others with severe hyperinsulinaemia and insulin resistance. It is suggested that at least some clinical features of MyD may be due to diminished overall effect of insulin or other trophic factors on cell metabolism.

INTRODUCTION

Myotonic muscular dystrophy (MyD) is a dominantly inherited disease that has hyperinsulinaemia and generalized insulin resistance among its most consistent features (Tevaarwerk and Hudson, 1977; Tevaarwerk *et al.*, 1979; Moxley *et al.*, 1980; Perurena *et al.*, 1981; Moxley *et al.*, 1984). Clinically, MyD affects many organ systems with features that include muscle wasting, myotonia, testicular atrophy (Harper *et al.*, 1972) and lens cataracts (Eshaghian *et al.*, 1978) that manifest to a variable degree during childhood or adult life. Although the dystrophic gene probably affects most and possibly all tissues the striking involvement of some, such as skeletal muscle and the tubular cells of the testes, is of interest because they are apparently more vulnerable to the dystrophic process than others.

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In addition, the offspring of affected mothers may show severe manifestations in the disorder referred to as congenital MyD (Harper, 1975*a*, *b*; Young *et al.*, 1981) or the neonatal MyD syndrome (Silver *et al.*, 1985).

Evidence of insulin resistance in MyD has been demonstrated by a number of studies. A diminished effect of exogenous insulin on the rate of fall of plasma glucose in MyD patients was initially shown by the insulin tolerance test (Barbosa *et al.*, 1974; Tevaarwerk and Hudson, 1977) and, more recently, a decrease in the effect of insulin on skeletal muscle and whole body glucose disposal rates has been demonstrated by euglycaemic insulin infusions (Moxley *et al.*, 1980, 1984). Also, disappearance of galactose from the circulation after an oral load is markedly increased and is accompanied by a corresponding rise in blood glucose suggesting hepatic insulin resistance and a requirement for an alternative glucose source (Tevaarwerk and Hudson, 1977). While seeking to explain insulin resistance a number of workers have observed reduced insulin binding to circulating monocytes (Festoff and Moore, 1979; Tevaarwerk *et al.*, 1979; Perurena *et al.*, 1981) but an explanation for altered binding has not been found. Nevertheless, compatible with this finding and the decrease in glucose disposal rates in response to exogenous insulin, glucose uptake into freshly biopsied MyD adipose tissue is diminished (Mably *et al.*, 1981).

Insulin resistance is often part of a vicious cycle in combination with hyperinsulinaemia and hypertriglyceridaemia and each of these can induce or enhance this cyclical process (Steiner and Vranic, 1982). Reports on circulating lipids in MyD have been variously described as showing elevation of both triglycerides and total cholesterol (Wakamatsu *et al.*, 1972) or no increase in either (Poffenbarger *et al.*, 1976). In the present report we describe plasma glucose, insulin and lipid levels in MyD subjects and a possible relationship of these to receptor binding of insulin and LDL to MyD fibroblasts in the attempt to characterize better the insulin resistance.

MATERIALS AND METHODS

Reagents

For tissue culture, receptor and membrane studies the following were used: Eagle's Minimum Essential Medium (MEM) with Earle's salts, L-glutamine, amino acids, trypsin-EDTA and 6-well culture plates were purchased from Flow Laboratories (Mississauga, Ontario); fetal bovine serum and 80 cm^2 culture flasks from GIBCO Laboratories (Burlington, Ontario); Na^{125}I and ^{125}I-insulin (receptor-grade) from New England Nuclear Corporation (Lachine, Quebec); L-(4,5-^{3}H)-leucine from Amersham (Oakville, Ontario); lactoperoxidase and glucose oxidase from Sigma Chemical Co. (St Louis, MO); all electrophoresis chemicals and protein determination reagents from BioRad Laboratories (Mississauga, Ontario); and other chemicals and supplies from Fisher Scientific Ltd (Don Mills, Ontario). Monocomponent porcine insulin was very kindly donated by Eli Lilly Co. (Scarborough, Ontario).

Tissue Culture

Fibroblast cultures were established from abdominal skin biopsies of 17 MyD and 17 age and sex-matched normal subjects with the patients' informed consent and the approval of the University of Western Ontario Standing Committee on Human Research. Cells were grown in Eagle's MEM supplemented with L-glutamine, nonessential amino acids, 23.8 mM $NaHCO_3$, 10% fetal bovine serum and Garamycin in a humidified 5% CO_2 atmosphere at 37° C (Lam *et al.*, 1983).

Plasma Studies

Subjects. In addition to MyD, two other myopathic disorders, facioscapulohumeral muscular dystrophy and amyotrophic lateral sclerosis, were studied as 'disease controls'. Each subject had a detailed examination, including an electromyographic study, to ensure diagnostic accuracy and to exclude other diseases such as diabetes mellitus. In each of the three groups the mean weight was within 12% of the ideal body weight. The age, sex and other significant criteria of three groups were as follows. (1) MyD: 4 females and 6 males with MyD ranging in age from 31 to 55 (mean 45·1) yrs were studied. Apart from 2 females (mother and daughter) all subjects were unrelated; the degree of disability varied markedly but all were ambulatory. (2) Facioscapulohumeral muscular dystrophy (FSH): 4 females and 7 males ranging in age from 16 to 52 (mean 31·6) yrs were studied. There were two families of 4 and 3 members each while the remainder were unrelated. All subjects were ambulatory. (3) Amyotrophic lateral sclerosis (ALS): none of the patients was related. 4 females and 7 males ranging in age from 42 to 67 (mean 55.3) yrs were studied. Five were wheelchair dependent.

Plasma insulin, triglycerides, cholesterol and lipoproteins. The concentration of insulin, triglycerides, cholesterol and lipoproteins were all determined on the same plasma samples. All subjects were fasted overnight (15 h) and none was diabetic. ^{125}I-insulin double antibody radioimmunoassay system (Bio-RIA, Montreal, Quebec) was used to measure plasma insulin concentration. Triglycerides and cholesterol were assayed using the Triglyceride-Enz test combination and cholesterol/CHOD-PAP C-system, respectively (Boehringer-Mannheim, Dorval, Quebec). Very low density lipoproteins (VLDL) were isolated from 4 ml of plasma by ultracentrifugation through 2 ml of buffered saline (0.15 M NaCl, 1 mM EDTA, 1 mM Tris, pH 7.4) in a Beckman 50.3 Ti rotor (40,000 rpm for 18 h at 12° C). The top 1 ml containing VLDL was assayed for triglyceride and cholesterol as described above. High density lipoproteins (HDL) were assayed for cholesterol following precipitation of plasma with heparin-manganese chloride (Warnick and Albers, 1978). Low density lipoprotein (LDL) cholesterol was calculated by difference. The infranatant (following ultracentrifugation), as well as whole plasma, was assayed for apolipoprotein B by electroimmunoassay according to the method of Reardon *et al.* (1981). The infranatant value was used as a measure of LDL apolipoprotein B. All samples for apolipoprotein B determination were treated with bacterial lipase (Boehringer-Mannheim, Dorval, Quebec) before assay to expose all antigenic determinants. Coefficients of variation of the above assay procedures (both within and between assays using the same procedure) were all less than 4% except the interassay procedure for LDL apolipoprotein B that was 9%. Apolipoprotein E phenotypes were determined by analytical isoelectric focusing electrophoresis of VLDL apolipoproteins as described by Huff and Telford (1984).

Whole Cell Radiolabelling

^{125}I labelling. For each experiment cultured fibroblasts from an age and sex-matched pair of MyD/control subjects were labelled with ^{125}I using a modification of the method of Hynes (1973). Seven to ten days after plating, six 100 x 20 mm petri dishes per subject were used (1.7–2.2 mg protein/subject at harvesting). Two dishes of cell monolayers from each subject were washed three times with phosphate-buffered saline (PBS) and then labelled for 8 min at room temperature in 5 ml PBS containing 25 μmol of glucose, 1 mCi Na^{125}I, 100 μg lactoperoxidase and 500 mU glucose oxidase. The reaction was stopped by the addition of 2 ml PBI (PBS made with NaI instead of NaCl). The cells were then rinsed twice with PBI and once with PBS. These dishes and the remaining four (also PBS washed) were pooled and used for the plasma membrane preparation as described below.

^{3}H labelling. This also was performed on cultured fibroblasts from age and sex-matched MyD/

control pairs. Six to nine days after plating, 10 μCi of L-(4,5-^{3}H)-leucine were added to each 100 × 20 mm petri dish of fibroblasts prepared in sextuplicate. They were then incubated for an additional 24 h. Cells were rinsed with PBS and the membrane prepared as described below.

Membrane Preparation

The fibroblast membranes were isolated and purified by a modification of the method of Thom *et al.* (1977). Cells were removed from dishes with PBS (minus Ca^{++} and Mg^{++}) containing 1 mM EDTA and collected by centrifugation. The supernatant, designated the 'EDTA' fraction was saved for study as described below. The pellet was resuspended in PBS, added slowly to an alkaline extraction solution and after 10 min a borate solution was added (Thom *et al.*, 1977). This preparation was centrifuged at 450 × g for 10 min after being filtered through nylon gauze. The supernatant was recentrifuged at 12 000 × g for 30 min at 2° C and this supernatant, designated the 'alkaline' (pH 10.2) fraction, was saved. The pellet was resuspended in PBS, layered on a 35% sucrose solution in PBS and centrifuged at 24 000 × g for 1 h at 2° C. The interface containing the plasma membrane fraction was removed by pipette, suspended in PBS and centrifuged at 100 000 × g for 10 min at 2° C to yield the 'membrane vesicle' fraction. The EDTA and alkaline fractions were dialysed against four changes of double distilled water, and then lyophilized for subsequent gel electrophoresis.

Polyacrylamide Gel Electrophoresis

Slab gels consisting of 5% stacking gel and 7.5%, 9%, or 8–16% (gradient) separating gel were run using a SDS-PAGE system similar to the method of Laemmli (1970). Gels were fixed overnight in 40% methanol and 10% acetic acid and stained using the silver stain method of Merril *et al.* (1981). After staining, the gels were dried and autoradiography using Kodak XAR-5 film was performed similar to the method of Fairbanks *et al.* (1965). Some gels were sliced into 4 mm sections and dissolved in 1.0 ml of 30% hydrogen peroxide and incubated at 55° C overnight. Iodinated samples were counted in a LKB 1280 ultragamma counter. ACS was added to ^{3}H-leucine samples and counted in a beta scintillation counter (Isocap/300).

Insulin Binding

Myotonic dystrophy and age and sex-matched control fibroblasts were plated in triplicate in 6-well culture plates seven days before the experiment. The monolayers (2.0–4.5 × 10^5 cells/well) were washed twice with phosphate buffered saline and then 0.1 ng ^{125}I-insulin in 1 ml of binding buffer was added. Different concentrations were used by the addition of unlabelled insulin to give total concentrations of 0.1, 1, 10, 100 and 1000 ng insulin/ml with 10 000 ng/ml used for nonspecific binding. The binding buffer used consisted of 50 mM Hepes, 0.12 M NaCl, 1.2 mM $MgSO_4$, 2.5 mM KCl, 10 mM glucose and 4% BSA at pH 8.0, 7.4 or 7.0 (Schilling *et al.*, 1979). The fibroblasts were incubated for 5 h in a 15° C waterbath. To stop the binding, 2° C binding buffer with no BSA was used in the washing procedure of Baldwin *et al.* (1981). To solubilize the cells, 1 ml of 1 N sodium hydroxide in 2% sodium carbonate was added and incubated for 2 h at room temperature. An aliquot was taken for counting to determine the amount of insulin associated with the fibroblasts. A separate aliquot was taken for protein assay.

For insulin-insulin receptor dissociation studies, matched pairs (plated at 2 × 10^5 cells/well seven days before the experiment) were incubated at 15° C with 0.1 ng ^{125}I-insulin per ml of binding buffer (pH 8.0) and, after 3 h, washed as described in the insulin binding procedure. The dissociation followed the method of Taylor and Leventhal (1983). Concentrations of 0, 20, 500, 5000, 50000 and 500000 ng/ml unlabelled insulin in the binding buffer (pH 8.0) were added for a second incubation of 0, 6, 15 and 30 min. The fibroblasts were again washed and solubilized with NaOH and counted as described above. The dissociation rate constant for insulin binding to MyD and control cells was calculated as described by Pollet *et al.* (1977).

Low Density Lipoprotein (LDL) Binding

LDL preparation and labelling. LDL was isolated from human plasma by ultracentrifugation in the 1.019 to 1.063 g/ml density fraction as described by Havel *et al.* (1955) and was labelled with ^{125}I by the iodine monochloride method of McFarlane (1958) as described by Huff and Telford (1985). The radiolabelled LDL was diluted to a specific activity of about 24 cpm/ng LDL-protein and had less than 2% free iodine in the preparation and less than 5% label in the lipids. The LDL was then stored at 4° C for no longer than one month and filtered before each use through a 0.22 μm Millipore filter. Following lipoprotein extraction the remaining plasma (density $>$ 1.215 g/ml) was dialysed in a NaCl-Tris-EDTA (pH 7.4) buffer to remove excess salts and was then clotted with 1000 units/ml thrombin to yield lipoprotein-deficient serum. This was used in the preincubation medium of cells preparatory to ^{125}I-LDL binding.

LDL binding and internalization. The methods of Goldstein *et al.* (1976) and Brown and Goldstein (1976) were used. Seven days before the experiment the cultured fibroblasts were plated in 6-well culture plates. The monolayers were lipid starved for 48 h (day 5) with 10% (5 mg/ml) human lipoprotein-deficient serum (HLDS) supplemented media (Goldstein *et al.*, 1976). The fibroblasts were incubated at 37° C for 5 h with ^{125}I-LDL in 1 ml of the HLDS media. A blank value was determined using corresponding ^{125}I-LDL in supplemented media with no cells. At the end of the incubation a sample of the medium was added to an equal volume of 20% trichloroacetic acid. Following the removal of free iodine by the addition of potassium iodide, hydrogen peroxide and chloroform, an aliquot of the aqueous phase of the trichloroacetic acid-treated sample was counted to determine the amount of LDL degraded by the cells. The fibroblast monolayers were rapidly chilled to 4° C to stop further uptake by washing 6 times using the standard procedure of Goldstein *et al.* (1976) with NaCl-Tris-bovine serum albumin (pH 7.4) buffer. One ml of a NaCl-Hepes-dextran sulphate (pH 7.4) solution was then added to the monolayer and incubated for 1 h at 4° C with shaking to release the bound LDL. An aliquot of this buffer was counted to determine the amount of LDL bound to the cell surface. One ml of 1 N NaOH in 2% Na_2CO_3 was added to the monolayer and incubated for 2 h at room temperature. A sample of this solution was counted to determine the LDL internalized by the fibroblasts.

LDL was also bound to cultured fibroblasts at 4° C for 2 h with a 30 min prechill (Brown and Goldstein, 1976). The media used in these experiments had no sodium bicarbonate but used 10 mM Hepes as the buffering agent. The amount of LDL bound and internalized by the cells was examined.

RESULTS

Plasma Insulin

Fasting plasma insulin was determined on the same samples as glucose, lipids and lipoproteins. As shown in Table 1 there was a significant elevation of plasma insulin in MyD at 181.1 ± 25.5 compared with the normal control value of 86.0 ± 3.7 pmol/l (mean ± SE). Insulin concentration in MyD was also significantly increased in relation to findings in FSH and ALS (82.2 ± 7.9 and 98.4 ± 11.9 pmol/l, respectively) that were in the normal range. In none of the three groups was there an increase in the fasting plasma glucose.

Plasma Triglycerides and Cholesterol

Plasma triglycerides in MyD were significantly increased at (mean ± SE) 274.3 ± 65.7 as compared with 110.9 ± 13.5 in FSH and 149.5 ± 23.3 mg/dl in ALS (Table 1). When compared by sex and age with the values reported by Rifkind and Segal (1983) on lipid distributions for the American population, MyD subjects fell

TABLE 1. FASTING PLASMA CONCENTRATIONS OF GLUCOSE, INSULIN, LIPIDS AND LIPOPROTEINS IN MYOTONIC DYSTROPHY (MyD), FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY (FSH) AND AMYOTROPHIC LATERAL SCLEROSIS (ALS)*

				MyD/control P values		
	MyD	*FSH*	*ALS*	*MyD/Normal*	*MyD/FSH*	*MyD/ALS*
Mean age (yrs)	45.1	31.6	55.3			
Male/female	6/4	7/4	7/4			
Glucose (mmol/l)**	5.2± 0.1	5.4±0.4	5.4± 0.3	n.s.	n.s.	n.s.
Insulin (pmol/l)**	181.1±25.5	82.2±7.9	98.4±11.9	< 0.001	< 0.005	< 0.025
Triglycerides†						
Total (mg/dl)	274 (127–421)	111 (81–141)	150 (98–201)	—	< 0.01	< 0.025
	[138 (50–290)]	[108 (43–230)]	[141 (55–295)]			
VLDL (mg/dl)	180 (32–328)	48 (28–68)	58 (29–86)	—	< 0.025	< 0.05
Cholesterol†						
Total (mg/dl)	210 (183–237)	172 (154–190)	179 (140–217)	—	< 0.025	n.s.
	[210 (156–270)]	[182 (137–245)]	[220 (164–283)]			
VLDL (mg/dl)	33 (5–62)	10 (6–15)	16 (4–29)	—	< 0.05	n.s.
LDL (mg/dl)	120 (98–143)	108 (92–124)	114 (77–150)	—	n.s.	n.s
	[140 (85–197)]	[117 (72–167)]	[143 (92–208)]			
HDL (mg/dl)	57 (46–68)	50 (40–60)	49 (42–55)	—	n.s.	n.s.
	[53 (31–75)]	[49 (32–70)]	[54 (32–79)]			
LDL apolipoprotein (mg/dl)**	102.0± 8.4	101.1±5.9	82.7±12.3	< 0.05	n.s	n.s.

* All data for each subject were obtained on the same plasma sample. ** Mean±SEM. Normal control values for glucose and insulin obtained on 40 subjects were 5.0±0.1 mmol/l and 86.0±3.7 pmol/l, respectively. LDL apolipoprotein B on 20 subjects was 84.3±4.0 mg/dl. † The values for triglycerides and cholesterol are the rounded mean values and the 5th and 95th centiles (bracketed). Normal lipid and lipoprotein reference values, as reported by Rifkind and Segal (1983), are shown below and correspond in age and sex to the MyD, FSH and ALS data.

into the upper range between the 5th and 95th centiles (50–290 mg/dl) whereas FSH and ALS were in the 50th centile range. In contrast to the triglyceride level the total plasma cholesterol concentration in MyD, FSH and ALS patients were within the normal range, close to the mean value reported by Rifkind and Segal (1983). As shown in Table 1 there were significant differences in some of the lipid and lipoprotein findings between MyD and FSH and ALS. For MyD/FSH the difference may be due, in part, to the younger ages of the FSH subjects.

Plasma Lipoproteins

Corresponding to the triglyceride concentration the plasma VLDL-triglyceride level of 179.6±65.4 mg/dl in MyD was significantly increased as compared with 48.1±8.9 mg/dl for FSH and 57.7±12.7 mg/dl for ALS (Table 1). There are no standard values for VLDL but the level reflects total triglyceride concentration. The same applies to plasma VLDL-cholesterol that, similar to total cholesterol, also was increased compared with the FSH value. LDL and HDL cholesterol values in the three groups of disorders were not different from one another and were within the normal range of the Rifkind and Segal (1983) reference values. The concentration of LDL apolipoprotein B in MyD was increased at 102.0±8.4 mg/dl compared with the normal value of 84.3±4.0 mg/dl but was not significantly different from FSH or ALS. FSH apolipoprotein B concentration (101.1±5.9 mg/dl) was also greater than normal ($P < 0.025$).

There was a significant correlation in MyD between the plasma insulin level and total triglycerides (r = 0.82, $P < 0.01$), insulin and VLDL-triglycerides (r = 0.76, $P < 0.05$) and insulin and VLDL-cholesterol (r = 0.81, $P < 0.01$). No correlation existed between insulin and the lipids or lipoproteins in FSH or ALS except in ALS where there was a direct relationship between insulin and HDL (r = 0.70, $P < 0.05$).

Type E Phenotyping

Like the MyD gene, the apolipoprotein E gene is located on chromosome 19 but its proximity to the MyD gene is uncertain (Francke *et al.*, 1984). The apolipoprotein E phenotypes were determined to ascertain whether the apolipoprotein E_2E_2 phenotype that is associated with type III hyperlipidaemia (Utermann *et al.*, 1977, 1984) and the E_4E_4 phenotype associated with hypercholesterolaemia (Francke *et al.*, 1984) are more prevalent in MyD than in FSH, ALS or the general population. We reasoned that if the apolipoprotein E and MyD genes were even loosely linked then MyD may be associated with a high frequency of the rarer isoforms of apolipoprotein E. VLDL apolipoprotein E phenotypes in the three groups of disorders were as follows (number of patients in brackets): MyD—E_3E_3 (5), E_3E_2 (3), E_4E_3 (2); FSH (3 not done)—E_3E_2 (3), E_3E_3 (2), E_4E_3 (2), E_4E_2 (1); ALS—E_3E_3 (6), E_4E_3 (2), E_2E_2 (2), E_3E_2 (1). Although the numbers of patients studied are low for this type of comparison, no major differences in the apolipoprotein E phenotypes were found in MyD compared with the normal population.

Insulin Binding

The results of insulin binding to MyD and control cultured fibroblasts under optimal binding conditions (pH 8.0, 15° C) and under conditions of lowered pH (7.0, 15° C) are shown in fig. 1. Under optimal conditions insulin binding capacity in the control group was (mean ± SE) 3.33 ± 0.49% of the total insulin added per mg cell protein (or 1.80 ± 0.24 pg/mg protein) and was greater ($P < 0.05$) than 2.27 ± 0.35% (or 1.22 ± 0.20 pg/mg protein) in MyD patients. The addition of 0.9 ng/ml unlabelled insulin produced a decrease in the binding of labelled insulin in the normal group to 1.71 ± 0.26% as compared with 1.17 ± 0.16% in MyD ($P < 0.05$).

At pH 7.4 there was a decrease in the insulin binding capacity of both control and MyD fibroblasts and at pH 7.0 binding to control cells was only 1.24 ± 0.15% and for MyD cells 0.83 ± 0.09% of the total insulin added (or 0.65 ± 0.15 and 0.41 ± 0.11 pg/mg protein, respectively), a decrease of over 60% from pH 8.0. At each hydrogen ion concentration, the difference in insulin binding to control and MyD cells remained significantly different (pH 7.4 $P < 0.01$; pH 7.0 $P < 0.025$). Overall, lowering the pH from 8.0 to 7.0 produced a pronounced and almost identical decrease in insulin binding to control and MyD cells indicating normal sensitivity of the receptor to alterations in the hydrogen ion concentration.

The dissociation rate of bound ^{125}I-insulin from insulin receptors in an insulin-free medium and in the presence of various concentrations of native insulin

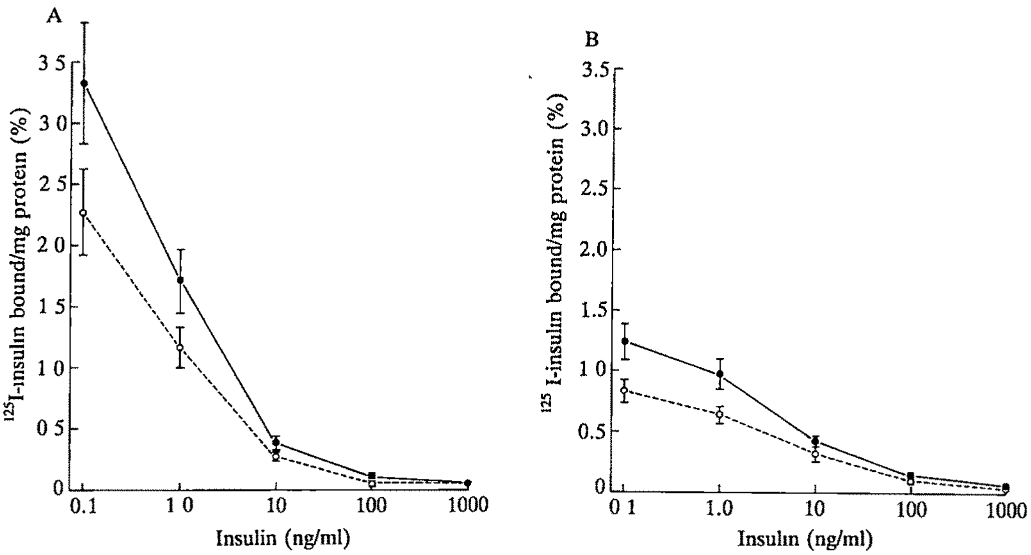

FIG. 1 Myotonic dystrophy (MyD, open circles) and age and sex-matched control fibroblasts (filled circles) were incubated with ^{125}I-insulin for 5 h at 15° C and at 3 different hydrogen ion concentrations The results (mean ± SEM) at pH 8.0 (A) (MyD/control pairs n = 10) and pH 7.0 (B) (MyD, n = 8; control, n = 12) only are shown. The initial binding at pH 7.4 (MyD, n = 5; control, n = 7) was 1.43±0.19 and 2.45±0.31% of the total insulin added per mg of cell protein for MyD and control, respectively.

was not significantly different in MyD compared with control fibroblasts. The initial dissociation rate constant for insulin binding to MyD fibroblasts was 2.5×10^{-4} S^{-1} and was not different from 2.7×10^{-4} S^{-1} for control cells. Thus no difference in the affinity of MyD and control insulin receptors, when assessed by the dissociation rate of bound insulin, was seen.

Low Density Lipoprotein Binding

A large number of matched control (n = 15) and MyD (n = 11) fibroblast paired experiments were studied at 37° C (pH 7.4). No significant difference in LDL binding, internalization and degradation between MyD and control cells was found (fig. 2). It is noteworthy, however, that there was a tendency to reduced LDL binding and internalization in the MyD cells as compared with the control cells by approximately 15 to 20%. LDL binding and internalization studies also were performed at 4° C (n = 6) and no differences between MyD and control cells were found (fig. 3).

Plasma Membrane Proteins

MyD and matching control fibroblast whole cell proteins were labelled with ^{3}H-leucine (5 pairs) and cell surface proteins with ^{125}I (25 pairs) in separate experiments. These were examined by SDS-PAGE and autoradiography. No significant differences were seen (fig. 4).

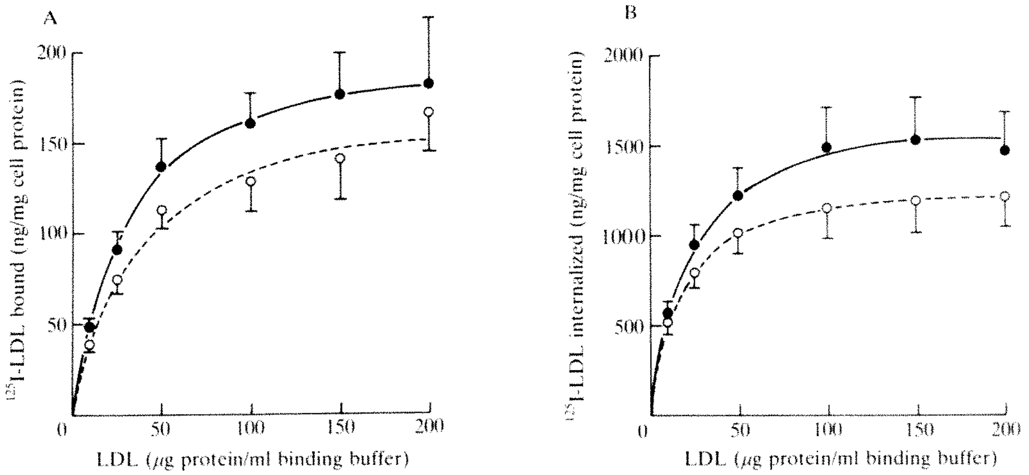

FIG. 2. Myotonic dystrophy (open circles, n = 11) and age and sex-matched control (closed circles, n = 15) cultured fibroblasts were incubated for 5 h at 37° C with ^{125}I-LDL (average of 24 cpm/ng). After incubation the medium was removed and trichloroacetic acid soluble material was measured (*see* text). After washing, dextran sulphate released (A, bound LDL) and dextran sulphate resistant (B, internalized LDL) ^{125}I-LDL were determined. The results are expressed as the mean ± SEM.

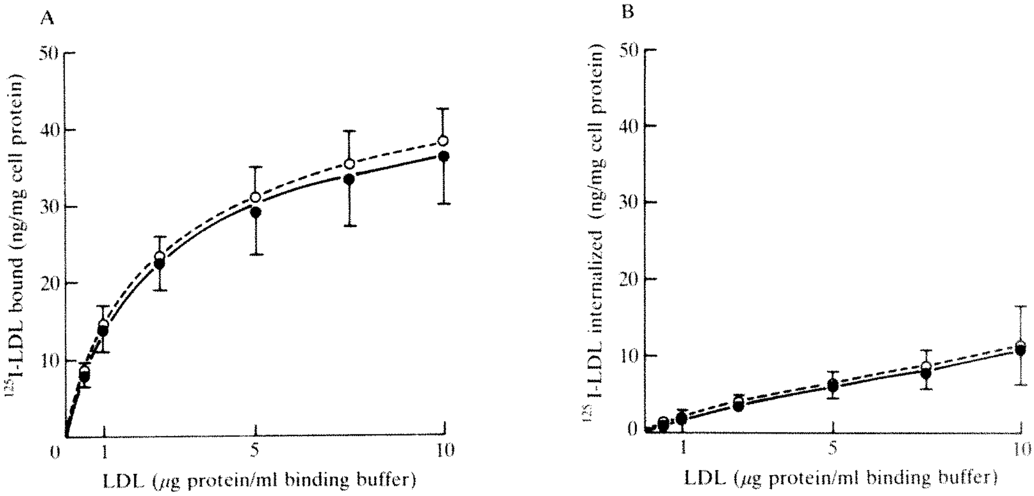

FIG. 3. Myotonic dystrophy (open circles, n = 6) and matched control (closed circles, n = 6) cultured fibroblasts were incubated for 2 h at 4° C with ^{125}I-LDL (average of 92 cpm/ng). Following incubation the medium was removed, the cells were washed and the dextran sulphate released (A, bound LDL) and dextran sulphate resistant (B, internalized LDL) ^{125}I-LDL were measured. The results are expressed as the mean ± SEM.

DISCUSSION

Fasting plasma insulin, triglycerides and VLDL were elevated whereas glucose, cholesterol, HDL and LDL were normal in MyD patients in this study (Table 1). Some investigators have reported normal fasting plasma insulin values in MyD

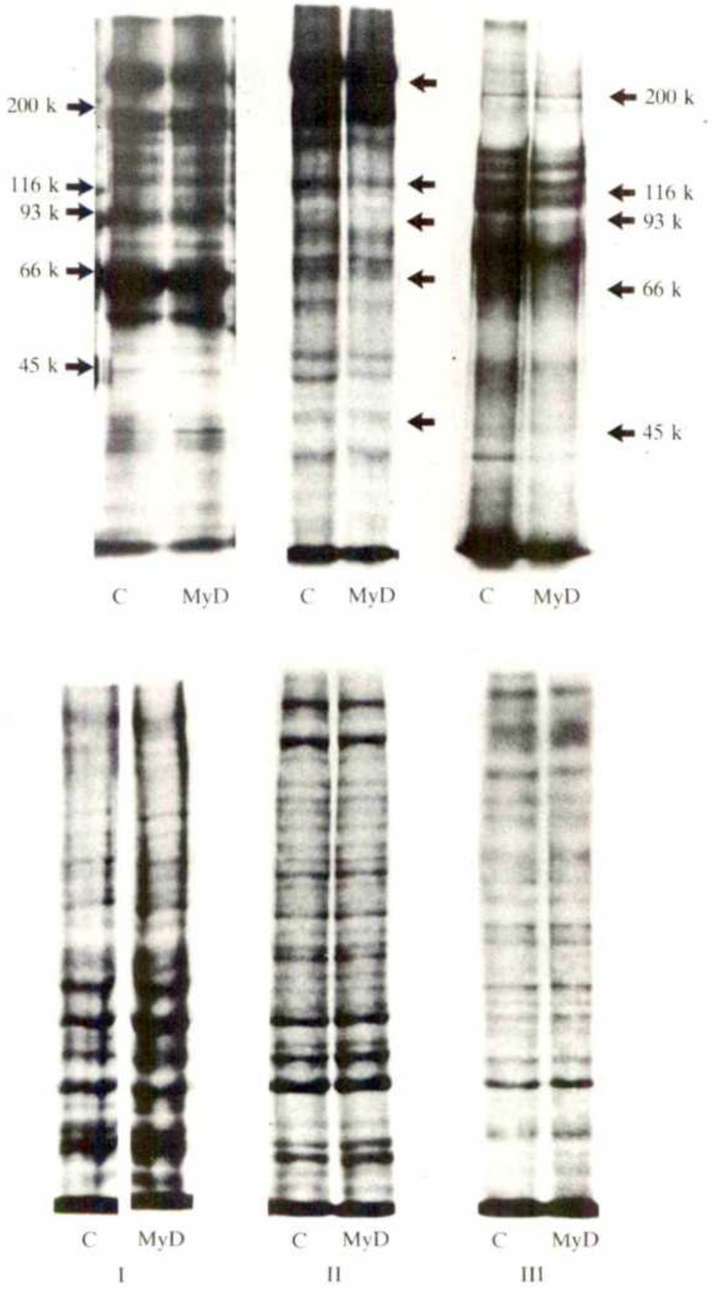

FIG. 4. SDS-PAGE autoradiographs of cultured fibroblast plasma membrane following whole cell ^{125}I (*top*) and ^{3}H-leucine (*bottom*) labelling. Myotonic dystrophy (MyD) and control (C) proteins were prepared in three fractions (*see* Methods) and each was run separately as shown in gels I (EDTA), II (alkaline—pH 10.2) and III (membrane vesicle). The numbers in the top figure are the molecular weights, in kilodaltons (k), of bands opposite arrows. Minor variations were present but there was no consistent difference from normal in any of the fractions.

but insulin is almost always excessively elevated in plasma following the administration of glucose (Tevaarwerk and Hudson, 1977; Moxley *et al.*, 1984). The hypertriglyceridaemia in MyD shows a direct relationship to hyperinsulinaemia ($r = 0.82$, $P < 0.01$). That this phenomenon is associated with MyD and not neuromuscular disease generally was demonstrated by a comparison with two disease controls, FSH and ALS, neither of which showed elevation of insulin or lipids despite a diminished capacity for glucose uptake due to muscle wasting. Insulin resistance has been demonstrated by various methods, most recently by means of euglycaemic insulin infusions (Moxley *et al.*, 1984), and it is likely that both the hyperinsulinaemia and hypertriglyceridaemia are further expressions of this phenomenon.

Reduced insulin binding to circulating monocytes has been found in MyD and there is a direct relationship between the reduced binding and insulin resistance (Tevaarwerk *et al.*, 1979). However, with circulating monocytes it can be difficult to decide whether a reduction in binding is due to an intrinsic cellular defect or a down-regulation of insulin receptors in response to hyperinsulinaemia. Because insulin binding to cultured MyD fibroblasts that have been incubated in an insulin-free medium was also diminished in our study (fig. 1), the alteration in binding must have been due, primarily, to a defect either in the insulin receptor or distal to this in the course of insulin metabolism. Binding affinity is a sensitive index of receptor function and may be altered by a structural defect of the insulin receptor (Taylor and Leventhal, 1983). Accordingly, we examined the dissociation rate of ^{125} I-insulin bound to MyD fibroblast receptors as a measure of binding affinity and found no difference from normal. Moreover, when the pH of the incubation medium was reduced from pH 8.0 to 7.0 to determine the sensitivity of the insulin receptor to conditions that normally lower its affinity (Hidaka *et al.*, 1981), insulin binding to both MyD and control cells was reduced to the same degree, that is, by about 60%. Thus, no difference from normal in the binding affinity of the MyD fibroblast insulin receptors was found which suggests that reduced binding may be due to reduced receptor numbers and, most likely, a cellular metabolic defect.

We found that, in contrast to insulin binding, LDL binding to cultured MyD fibroblasts was not significantly altered (fig. 2). There was, however, a trend to reduced LDL binding, internalization and degradation by 15% to 20% in MyD cells when incubated at 37° C. The difference in LDL binding between MyD and control cells at 37° C, while not statistically significant, may be due to marginally reduced LDL metabolism since there was virtually no difference in binding when cell metabolism was inhibited by incubating cells at 4° C (fig. 3). In support of altered cell metabolism in MyD, glucose catabolism in freshly biopsied MyD adipose tissue at 37° C is also reduced (Mably *et al.*, 1981). Nevertheless, the finding of essentially normal LDL binding is in agreement with the observed normal plasma levels of LDL and cholesterol (Table 1) because, in known LDL receptor-defective disorders with reduced binding, plasma LDL and total cholesterol are markedly elevated (Brown and Goldstein, 1976). The ratio of the LDL internalized and degraded to the amount bound to MyD fibroblasts, a calculation that is used to define the 'internalization index' of internalization-defective mutations, was also normal.

The genes for MyD, the LDL receptor, the insulin receptor and apolipoproteins E and C-II, are all located on chromosome 19 (Francke *et al.*, 1984; Shaw *et al.*, 1985; Straus *et al.*, 1985). The proximity of the genes for apolipoprotein E and MyD is not known. Accordingly, we explored the possibility that, if linkage were close, the rarer isoforms of apolipoprotein E might be more frequent in MyD. No major differences from normal were found. On the other hand, the apolipoprotein C-II (activator of lipoprotein lipase) gene is closely linked to the MyD locus on chromosome 19 (Shaw *et al.*, 1985) and it is known that a genetic absence of apolipoprotein C-II leads to marked hypertriglyceridaemia (Breckenridge *et al.*, 1978). Thus, it is possible that if a functional defect in the apolipoprotein C-II gene were present it would be transmitted with the MyD gene. We found, on visual examination of the isoelectric focusing gels, no gross deficiency in apolipoprotein C-II (data not shown). Nevertheless, further studies are required to determine whether there is a high frequency of apolipoprotein C-II variants, that may be nonfunctional, in MyD.

In addition to enhancing glucose and amino acid uptake, insulin also augments various aspects of cell metabolism. This action includes, in whole or part, the functions of plasma membrane hexose transport and stimulation of nucleic acid and protein synthesis by insulin mediators that are thought to be released upon insulin binding to its receptor (Kahn *et al.*, 1981; Jarett *et al.*, 1985). A deficiency of insulin action in its multiple roles might provide an explanation for some adult features and metabolic abnormalities, such as impaired muscle protein synthesis, in MyD (Halliday *et al.*, 1985). As shown in Tables 2 and 3, some evidence in support of this view is obtained when comparisons are made of the clinical features of MyD with other inherited insulin-resistant diseases.

Inherited insulin-resistant diseases can be differentiated, clinically, into two groups on the basis of increased or decreased somatotrophic features. In the *hyper*somatotrophic group (Table 2) are acanthosis nigricans type A, congenital generalized lipodystrophy, leprechaunism and the Rabson-Mendenhall syndrome. Their hypertrophic features consist of increased early body growth, decreased body fat, genital enlargement, hirsutism, acanthosis nigricans, hyperkeratosis and loose or thickened skin. All have severe insulin resistance and all but congenital generalized lipodystrophy have moderate to severe hyperinsulinaemia. In the *hypo*somatotrophic group (Table 3) to which MyD belongs are, in addition, the syndromes of Alstrom, Werner, Cockayne, Prader-Willi and ataxia telangiectasia. In contrast to the hypersomatotrophic syndromes the features in this group consist of short stature, impaired muscular development or wasting, hyperostosis of the skull, small external genitalia, hypogonadism, testicular atrophy, cataracts, pigmentary retinopathy, early greying and loss of hair and premature ageing. All disorders in this category have mild insulin resistance and mild hyperinsulinaemia except ataxia

TABLE 2 CLINICAL AND LABORATORY FEATURES OF THE INHERITED INSULIN RESISTANT DISEASES—HYPERSOMATOTROPHIC GROUP

Features	*Acanthosis nigricans type A*	*Congenital generalized lipodystrophy*	*Leprechaunism*	*Rabson-Mendenhall syndrome*
Inheritance	Probably autosomal recessive	Autosomal recessive	Autosomal recessive	Autosomal recessive
Age of clinical onset	Infancy or early childhood	Early childhood	Infancy	Infancy
Life expectancy*	Normal	Normal	3 wks to 8 yrs (mean, 9 mo)	Usually less than 9 yrs
Intellect	Normal	Often retarded	Retarded	Normal
Nervous system	Normal	Normal	Normal, cerebellar hypogenesis and absence of corpus callosum reported	Pineal hyperplasia, otherwise normal
Sexual development	Enlarged clitoris (female)	Moderate enlargement of clitoris and penis	Enlarged genitalia and gonads (both sexes)	Enlarged genitalia (both sexes)
Musculature	Normal, masculine habitus in females	Well developed, muscular hypertrophy	Normal	Normal
Body growth	Accelerated early growth	Accelerated early growth	Growth retardation but prominent breasts	Increased early growth
Skin	Acanthosis nigricans	Acanthosis nigricans	Acanthosis nigricans, loose skin, hyperkeratosis	Acanthosis nigricans, thickened skin and nails
Eyes	Normal	Normal	Normal	Normal
Hair	Hirsutism	May have hirsutism	Hirsutism	Hirsutism
Teeth	Normal	Normal	Normal	Early dentition (age 2 to 4 yrs)
Endocrine function**	Moderate hyperinsulinaemia, severe insulin resistance, elevated plasma testosterone	Mild hyperinsulinaemia, severe insulin resistance, hypertriglyceridaemia, elevated serum ACTH and prolactin	Severe hyperinsulinaemia, severe insulin resistance, fasting hypoglycaemia	Severe hyperinsulinaemia, severe insulin resistance
Insulin binding	Reduced (fibroblasts)	Normal or reduced (monocytes and fibroblasts)	Reduced (fibroblasts)	Reduced (fibroblasts)
Glucose uptake				
(a) basal	—	Increased (fibroblasts)	Normal (fibroblasts)	—
(b) with insulin	—	Normal (fibroblasts)	Reduced (fibroblasts)	—
Glycogen synthase				
(a) basal	Normal (fibroblasts)	Increased (fibroblasts)	Normal (fibroblasts)	—
(b) with insulin	Reduced (fibroblasts)	Reduced (fibroblasts)	Normal or increased (fibroblasts)	—
DNA· thymidine incorporation with insulin	Reduced (fibroblasts)	—	Reduced (fibroblasts)	—
Comments	All reported subjects are female, small cystic ovaries	Absence of body fat, euthyroid hypermetabolism	Decreased subcutaneous fat, increased hepatic glycogen, elfin facies, rugated orifices	Organomegaly, death due to pineal tumour with hydrocephalus, premature ageing
References	Kahn *et al* (1976) Bar *et al.* (1980) Podskalny and Kahn (1982 *a, b*)	Köbberling (1976) Oseid *et al* (1977) Howard *et al* (1981) Franklin *et al.* (1984) Golden *et al.* (1985)	Schilling *et al* (1979) Rosenberg *et al* (1980) Knight *et al* (1981) Taylor *et al* (1982*b*)	West *et al* (1975) West and Leonard (1980) Taylor *et al* (1983)

* Excluding effects of diabetes mellitus ** Mild, moderate and severe hyperinsulinaemia are arbitrarily set with fasting plasma insulin of < 100, 100–800 and > 800 μU/ml, respectively

telangiectasia in which these features are moderate. Ataxia telangiectasia has antibodies to the insulin receptor which may explain the difference in insulin resistance in this disease since insulin binding to cultured fibroblasts is normal (Taylor *et al.*, 1982*a*). Laboratory studies in the two somatotrophic groups are difficult to interpret because the findings, apart from insulin receptor binding studies, are limited or highly varied (Tables 2, 3). However, in vitro insulin receptor binding in all disorders of both groups where it has been examined is reduced. Despite the overall reduced insulin binding the distinctive clinical features between the two groups of

TABLE 3. CLINICAL AND LABORATORY FEATURES OF THE INHERITED INSULIN-RESISTANT DISEASES—HYPOSOMATOTROPHIC GROUP

Features	*Alstrom*	*Myotonic dystrophy*	*Werner*	*Cockayne*	*Prader-Willi*	*Ataxia telangiectasia*
Inheritance	Autosomal recessive	Autosomal dominant	Autosomal recessive	Autosomal recessive	Probably autosomal recessive	Autosomal recessive
Age of clinical onset	Infancy	Infancy to adolescence	Childhood to adolescence	Infancy	Infancy	Infancy to 6 yrs
Life expectancy*	Normal	Normal	20 to 65 yrs	Limited; early adulthood	Normal	Reduced
Intellect	Normal or retarded	Normal or retarded	Often retarded	Severely retarded	Retarded	Sometimes retarded
Nervous system	Nerve deafness	Normal	Normal	Microcephaly, ataxia, nerve deafness	Strabismus	Ataxia, chorea
Sexual development	Testicular atrophy	Testicular atrophy	Testicular atrophy, small external genitalia (both sexes)	Sexual retardation (both sexes)	Small external genitalia, hypogonadism (both sexes)	Sexual infantilism, hypogonadism (both sexes)
Musculature	Normal	Neonatal hypotonia, distal atrophy and myotonia	Distal muscle wasting	Small mass	Neonatal hypotonia	Muscle atrophy
Body growth	Scoliosis, hyperostosis of skull	Hyperostosis of skull	Short stature due to growth failure	Short stature, hyperostosis of skull	Short stature, delayed bone age, small hands and feet	Growth retardation
Skin	Acanthosis nigricans	Normal	Atrophic, ulcers, mild hyperpigmentation	Rough, dry, mild hyperpigmentation	Normal	Telangiectases, atrophic, pigmented
Eyes	Cataracts, pigmentary retinopathy	Cataracts, pigmentary retinopathy	Cataracts, pigmentary retinopathy	Cataracts, pigmentary retinopathy	Normal	Normal
Hair	Baldness	Baldness	Early greying, baldness	Normal	Normal	Early greying
Teeth	Normal	Normal	Normal	Carious	Carious	Normal

Endocrine function**	Usually mild hyperinsulinaemia, mild insulin resistance, hypertriglyceridaemia	Mild hyperinsulinaemia, mild insulin resistance, hypertriglyceridaemia	Mild hyperinsulinaemia, mild insulin resistance	Mild hyperinsulinaemia, mild insulin resistance, type II hyperlipoproteinaemia	Mild hyperinsulinaemia, mild insulin resistance, elevated free fatty acids	Moderate hyperinsulinaemia, moderate insulin resistance
Insulin binding	—	Reduced (monocytes and fibroblasts)	Reduced (fat cells)	—	Reduced (monocytes)	Normal (fibroblasts), antibodies to insulin receptor
Glucose uptake						
(a) Basal	—	Reduced (adipose tissue)	—	—	—	—
(b) With insulin	—	Reduced (adipose tissue)	Reduced (fat cells)	—	—	—
Glycogen synthase						
(a) Basal	—	—	—	—	—	—
(b) With insulin	—	—	—	—	—	—
DNA: thymidine incorporation with insulin	—	—	—	—	—	—
Comments	Nephropathy	Hypercatabolism of IgG and sometimes decreased IgA	Decreased subcutaneous fat, neoplasms, vascular disease, progeria similar to Rothmund's syndrome	Skin photosensitivity, may have intracranial calcification and peripheral neuropathy, progeria	Marked obesity, chromosomal abnormality (chromosome 15) reported in a number of cases	Lymphoreticular neoplasia, IgA and IgE deficiency, progeria, ovarian agenesis
References	Weinstein *et al* (1969), Goldstein and Fialkow (1973); Edwards *et al* (1976)	Tevaarwerk *et al* (1979); Mably *et al* (1981); Moxley *et al* (1984), Silver *et al* (1985)	Field and Loube (1960); Epstein *et al.* (1966); Blohmé and Smith (1979)	Neill and Dingwall (1950); Macdonald *et al* (1960); Fujimoto *et al.* (1969)	Zellweger and Schneider (1968), Sareen *et al* (1975), Bray *et al.* (1983); Kousholt *et al.* (1983); Kousseff and Douglass (1982)	Bar *et al* (1978); Cornforth and Bedford (1985)

* Excluding effects of diabetes mellitus. ** Mild, moderate and severe hyperinsulinaemia are arbitrarily set with fasting plasma insulin of < 100, 100–800 and > 800 μU/ml, respectively.

insulin-resistant diseases suggest that differences between them may be due to the influence of insulin or other trophic factors on cell growth and metabolism. In the *hyper*somatotrophic group the marked elevation of circulating insulin may have an excessive trophic influence upon cell development, despite severe insulin resistance, whereas in the *hypo*somatotrophic group, including MyD, the effect of insulin may be diminished.

Finally, in the course of our studies we were interested in excluding a major cellular protein defect, especially of cell surface membranes. No significant difference between MyD and control fibroblast plasma membrane and cytoplasmic proteins, as determined by radiolabelling and SDS-PAGE, was seen. However, this does not rule out functional protein or peptide abnormality.

In summary, in an enquiry into insulin resistance in MyD, we studied plasma glucose, insulin, lipids and lipoproteins and attempted to correlate the findings with insulin and LDL binding to cultured MyD fibroblasts. MyD subjects showed hyperinsulinaemia and hypertriglyceridaemia and reduced binding of insulin to fibroblasts. Insulin receptor binding affinity was normal. LDL binding was within the normal range. MyD appears to share features with a number of other inherited insulin-resistant diseases with mild hyperinsulinaemia and insulin resistance. It is suggested that some of the features of MyD may be due, in part, to a marked decrease of normal stimulatory effects of insulin or other trophic factors on cell metabolism.

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REGIONAL THRESHOLD CONTRAST SENSITIVITY WITHIN THE CENTRAL VISUAL FIELD IN OPTIC NEURITIS

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SUMMARY

Contrast sensitivity was measured at nine locations within the central 10° of the visual field in cases of recovered optic neuritis having varying degrees of residual deficit. A sample of 82 patches of visual field was obtained in 14 cases. Circular patches of vertically orientated sinusoidal gratings, 2.5° in diameter, were used. The gratings were modulated in time at 8 Hz and the effect of spatial frequency on the threshold loss determined at each visual field location. As anticipated from what is known of visual field changes in the disorder there was considerable variation in the magnitude of the contrast threshold elevation at different locations in the visual field in any one case. The variability was more marked in cases with greater overall deficit.

Three types of spatial loss were encountered. The most common was a loss which increased at higher spatial frequencies, found in 65 of the 82 patches of visual field examined. In 11 the loss was unaffected by spatial frequency and in the remaining 6 the loss was maximal at an intermediate spatial frequency. There was no instance of a loss maximal at low spatial frequencies. Overall the results indicate that sensitivity to higher spatial frequencies is more likely to be impaired following an attack of optic neuritis. In the combined results the effect of spatial frequency on the threshold elevation was statistically significant at all eccentricities ($P < 0.001$).

Analysis of the combined results revealed no difference in the mean contrast sensitivity loss at eccentricities of zero, 3.75° or 7.5° for intermediate and low spatial frequencies. There is no evidence from these results to suggest that the central foveal projection (papillomacular bundle) is more likely to be affected following an attack of optic neuritis than the projections of other eccentricities within the central 10° as far as mechanisms subserving luminance vision are concerned at these spatial frequencies. Overall there was slightly greater reduction in acuity within the central 5° than at 7.5° eccentricity ($P < 0.05$). This may be accounted for by the finding that higher spatial frequencies are more affected, rather than being related to eccentricity per se.

INTRODUCTION

In recent years a number of investigators have applied the threshold contrast sensitivity technique to the study of the visual deficit produced by optic neuritis and multiple sclerosis (MS) (*see* Regan, 1984; Hess and Plant, 1986, for recent review articles). An important aspect of this work has been to determine the effect of the

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spatial frequency of the visual stimulus on the visual loss. There is some evidence to suggest that there are within the human visual system functional mechanisms or 'channels' sensitive to a limited range or 'bandwith' of spatial frequencies (Campbell and Robson, 1968; Blakemore and Campbell, 1969). It has been inferred from spatial frequency discrimination experiments at detection threshold that there is a minimum of seven such channels subserving human vision (Watson and Robson, 1981). The receptive field properties of ganglion cells and of neurons at higher levels in the visual system can be described in terms of spatial frequency selectivity (*see* Robson, 1975, 1986, for review articles). Any evidence for a spatial frequency specific property of the visual deficit in optic neuritis might therefore indicate a neural specificity of the disorder and contribute towards our understanding of the pathological process.

Previous studies of the spatial contrast sensitivity function in both MS (Regan *et al.*, 1977; Bodis-Wollner *et al.*, 1979) and optic neuritis (Frisén and Sjöstrand, 1978; Zimmern *et al.*, 1979; Hess and Plant, 1986) have shown that the deficit in contrast sensitivity in these conditions is frequently spatial frequency dependent in that the magnitude of the threshold elevation varies with spatial frequency. The pattern of loss found in individual cases, however, is variable; high, low or medium spatial frequencies may be relatively more affected or all spatial frequencies may be evenly affected. Of these possibilities a low frequency loss is the least common but all occur.

We have argued elsewhere (Hess and Plant, 1986) that any of these four varieties of spatial loss may be accounted for by regional variations in the loss of contrast sensitivity within the area of visual field tested. Nonuniform involvement of the visual field is the rule in optic neuritis (both acutely and following recovery) and in MS. The pattern of loss found is highly variable (Nikoskelainen, 1975; Harms, 1976; Perkin and Rose, 1979; Patterson and Heron, 1980). Patchy involvement of the optic nerve is to be expected from what is known of the pathology of optic neuritis (largely inferred from postmortem studies of MS). The demyelinating lesions themselves occur in circumscribed plaques (Dawson, 1916), the size of which in the optic nerve is variable (McDonald, 1977; Ulrich and Groebke-Lorenz, 1983). Areas of both patchy and complete demyelination are seen and ultrastructural studies have shown that a range of abnormalities may be seen on different fibres within the same lesion (Prineas and Connell, 1978).

Dendritic field size of primate retinal ganglion cells, which determines receptive field size and hence spatial frequency selectivity, is monotonically related to eccentricity (*see*, e.g., the neurophysiological findings in the cat of Cleland *et al.*, 1979, and the anatomical studies of Perry *et al.*, 1984, in the primate). Furthermore, ganglion cell axons in the optic nerve are organized, at least to a first approximation, retinotopically, as was shown by, amongst others, Henschen (summarized in Traquair, 1948) and Polyak (1957). In a simulation study (Hess and Plant, 1986) we have demonstrated that a deficit maximal in the centre of the visual field will give rise to a contrast sensitivity deficit maximal at high spatial frequencies; that a parafoveal deficit will predominantly affect medium spatial frequencies; and that a peripheral deficit sparing the fovea will cause a low frequency loss. Similar results were obtained by Kelly (1984) using circular concentric cosine patterns.

It is therefore uncertain whether losses specific for spatial frequency reported in optic nerve demyelination using relatively large field sizes and central fixation are truly spatial frequency specific or retinal locus specific. As yet there is no evidence to indicate in any individual case which of these two possibilities is the likely explanation for such deficits. Distinguishing between these is not a straightforward exercise and there is no reason to suppose that *both* factors may not play a part. The aim of this study has been to attempt to reduce the confounding influence of the distribution of the anomaly across the visual field by exploring a number of regions of the visual field using small (2.5° diameter) grating patches. This approach necessarily involves a compromise because as the area of a grating (or more specifically the number of cycles of the grating) is reduced, it becomes more localized in the visual field but less localized in spatial frequency. As we wished to study the contrast sensitivity loss within defined regions of the visual field we have chosen to keep the area of the stimulus constant. At the lower spatial frequencies the spatial frequency content of the stimulus becomes broader as a consequence. The technique remains preferable to the use of spots, however, which are very poorly localized in spatial frequency and may therefore be detected by any one of a range of spatially tuned mechanisms. The theoretical considerations arising from this compromise are considered in the Discussion.

Eighty-two patches of visual field within the central 10° have been sampled in 14 cases of recovered optic neuritis; the acute phase of the disorder has not been studied. A large sample was considered necessary in view of the extreme heterogeneity of the disorder, both between and within individuals. The results may then allow a confident statement as to whether, overall, there is a tendency for a differential effect on optic nerve function that is dependent upon spatial frequency. We have also been able to assess quantitatively the extent to which eccentricities within the central 10° may be differentially affected in the disorder. The latter objective was considered of importance in view of the generally held belief that the central foveal projection in the optic nerve (the 'papillomacular bundle') is especially vulnerable in demyelinating optic nerve disease.

METHODS

Apparatus

Vertical gratings with sinusoidal luminance profiles were generated digitally on a specially constructed oscilloscope screen (Joyce screen) having a green (P_{31}) phosphor. The screen was masked with matt white cardboard to provide a circular aperture subtending 3° in diameter at the viewing distance of 456 cm. In addition, the edges of the aperture were 'softened' by an annulus of tracing paper having an internal diameter of 2.5° and an external diameter of 3° of visual angle (*see* fig. 1A). The tracing paper reduced screen contrast roughly by a factor of six. Henceforward the dimensions of the aperture referred to are measured from the inner edge of the tracing paper. The space-averaged luminance of the screen was 200 cd/m^2 and the surround illuminated to be of approximately the same

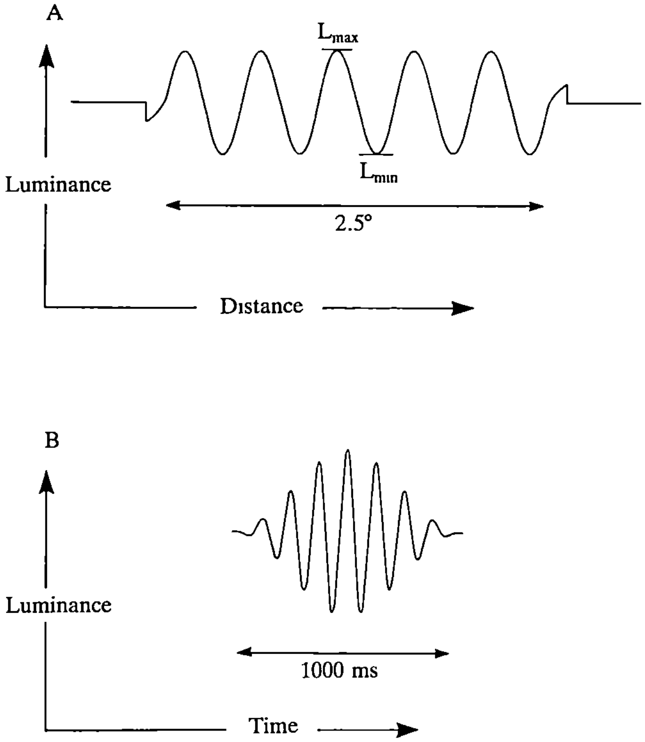

FIG. 1. The upper diagram (A) shows the luminance distribution in space of the visual stimulus used in this investigation. Luminance is plotted against distance in degrees of visual angle across the diameter of the aperture at right angles to the bars of the sinusoidal grating. The surround is at the same luminance as the mean luminance of the grating. Vignetting of the grating was achieved by 'softening' the contrast at the edge of the grating by means of an annulus of tracing paper 0.25° in width as shown above (*see* Methods). The grating shown here has a spatial frequency of 2 c/deg. L_{max} and L_{min} indicate, respectively, the peak and trough luminances of the grating. The lower diagram (B) shows the luminance change in time as it would appear if measured at, say, one of the peaks of the spatial waveform shown above. The grating stimuli used in this study were counterphase-modulated sinusoidally at 8 Hz and presented in a raised cosine temporal envelope 1 s in duration. The two luminance scales are arbitrary and not equivalent.

luminance and hue (although lower saturation). The frame rate of the oscilloscope was 200 Hz. The contrast of the grating was conventionally defined as $\frac{L_{max}-L_{min}}{L_{max}+L_{min}}$, where L_{max} and L_{min} are respectively the luminances at the peaks and troughs of the grating (*see* fig. 1A). Contrast was calibrated using a United Detector Technology photodiode and found to be linearly related to input voltage up to 99% contrast. The contrast of the grating could be varied in 0.5 dB steps ($dB = 20 \log C^{-1}$, where C = Contrast; *see* also caption to Table 2) by a digital attenuator controlled by a 6809 Motorola microprocessor. The computer also controlled the function generator which determined the spatial and temporal frequencies of the stimulus. As well as determining the spatial and temporal frequencies and the contrast of the stimulus, the computer monitored the subject's responses (button presses) and controlled the experiment.

In all the experiments the stimulus was counterphase-modulated sinusoidally in time at 8 Hz and presented in a raised cosine temporal window. The peak of the cosine window coincided with the peak of the stimulus temporal waveform and its total duration was 1 s (*see* fig. 1B). The spatial frequencies used were 0.5, 1, 2, 4, 8 and 16 cycles per degree (c/deg). Spatial frequency is defined as the number of cycles of the grating occurring in 1° of visual angle (*see* fig. 1A).

Patients and control subjects viewed the stimulus monocularly in a well lit room. The viewing distance was 456 cm. Optical correction was worn where necessary and confirmed to be optimal. Natural pupils were employed. When the screen was viewed centrally no fixation target was employed other than the screen itself. For eccentric viewing a fixation light was positioned 3.75 or 7.5° from the centre of the screen along the horizontal or vertical meridians. The nine regions of the visual field examined are represented in fig. 2.

Experimental Procedure

Threshold contrast sensitivity (the reciprocal of threshold contrast) was determined by a method of limits. A two-alternative forced choice test procedure was employed. The onset of each of two consecutive presentation intervals was signalled by an audible tone. Each interval was 1 s in duration. Either the first or the second interval (randomly assigned by the computer program) contained a grating stimulus and in the other the screen was blank but had the same mean luminance. The subject's task was to identify in which interval the grating had appeared. Feedback was given in the form of different tones to indicate to the subject whether his response had been correct or incorrect.

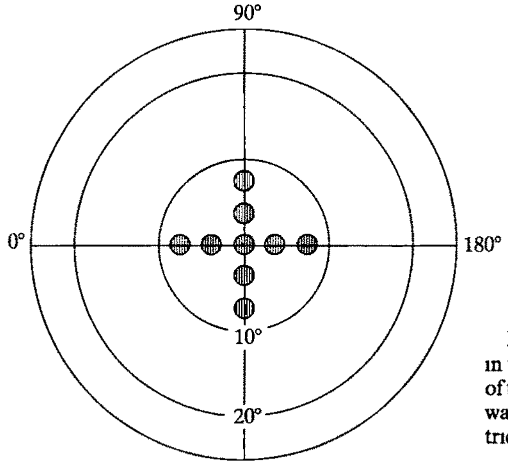

FIG. 2. The nine regions of the central visual field examined in the control and patient populations are shown. The centre of the screen, which subtended 2.5° of visual angle in diameter, was positioned at zero eccentricity or at 3.75 or 7.5° eccentricity along the horizontal and vertical meridians.

In each test run three spatial frequencies were randomly interleaved to minimize the effects of practice. All three gratings were initially shown at an easily visible contrast level. If the subject's response was correct then the next time the grating of that spatial frequency was shown it was at a slightly lower contrast level (in 0.5 dB steps). When the subject's response was incorrect the grating was next shown at a much higher contrast level (in 5 dB steps) such that it would be clearly visible, thus initiating the 'staircase' again. The computer ignored the first two incorrect responses or 'reversals' and stored the subsequent five contrast levels at which the subject had failed to respond correctly. Contrast sensitivity was taken to be the reciprocal of the mean of the five stored contrast values.

Subjects were tested in two sessions on two different days. In the first session zero eccentricity and the 4 regions of the field at 3.75° eccentricity were examined. In the second session the visual field loci at 7.5° were tested and some results from the first session were repeated to determine the repeatability of the normal and abnormal results. Thresholds obtained on the two days differed by no more than 2 dB in the control subjects although there was more variability in some of the optic neuritis cases.

Care was taken to ensure accurate fixation. The brightness of the fixation target was adjusted to be

TABLE 1. CLINICAL DETAILS OF THE PATIENTS ALL WERE CASES OF UNILATERAL (12) OR BILATERAL SEQUENTIAL (2) OPTIC NEURITIS

Case	*Age (yrs)*	*Acuity*	*Ishihara*[1]	*Disc*	*RAPD*[2]	*Visual field*[3]
1 (D.M.)	25	6/36	12	Pale	Yes	Central scotoma
2 (E.O.)	33	6/60	12	Pale	Yes	Central scotoma
3 (I.C.)	23	6/9	4	Pale	Yes	Full
4 (K.T.)	36	6/5	0	Pale	Yes	Full
5 (C.S.)	34	6/9	0	Pale	No	Full
6 (I.W.)	24	6/9	11	Pale	Yes	Not done
7 (E.R.)	28	6/6	0	Normal	No	Full
8 (J.F.)	40	6/5	2	Pale	No	Full
9 (S.B.)	30	6/6	1	Normal	No	Full
10 (R.B.)[4]	31	6/9	0	Pale	No	Not done
11 (C.R.)[4]	36	6/9	8	Pale	Yes	Paracentral scotoma
12 (D.N.)[4]	24	6/12	1	Pale	Yes	Paracentral scotoma
13 (P.S.)[4]	29	6/6	12	Pale	Yes	Not done
14 (G.R.)[4]	37	6/5	P[5]	Normal	Yes	Full

[1] Number of errors (maximum 12). [2] Relative afferent pupillary defect. [3] Bjerrum screen 5/2000 white target. [4] Patients used for central field examination only. [5] Protanomalous.

clearly visible by the subject. A chin rest was provided. The subject took up fixation just before pressing a button to initiate the stimulus presentation and was only required to maintain fixation for 2 s—the duration of the two presentation intervals. The subject then responded with a button press and was able to relax until he/she was ready to take up fixation again and initiate the next presentation. The experimenter was positioned alongside the test display facing the subject and was able to witness whether, at least, a gross eye-movement had taken place and was able to reject any response following an eye-movement. The SDs of the threshold settings did not differ significantly between results obtained with central and with eccentric fixation for patients or controls and it is not considered that inaccuracies of fixation have significantly affected the results.

Selection of Subjects

Ten control subjects were used, all of whom were inexperienced at visual psychophysics and did not differ significantly in either age or sex distribution from the patient group. The patients had all had an attack of optic neuritis, which was unilateral in 12, more than four months before testing. Some had had recurrent disease; 2 had bilateral disease which had been sequential. Optic neuritis was defined as visual impairment of subacute onset with recovery for which no specific cause (such as vascular or toxic disorders) was found. Further details are shown in Table 1. None of these patients showed clinical evidence of neurological disease outside the visual system at the time of testing and, in particular, none had any eye movement or motor disorder which may have affected their ability to carry out the test procedure. In 9 patients, all 9 visual field loci were examined. In 1 (Case 2) the 5 loci along the horizontal meridian only were tested and in a further 5 only the central visual field was tested (Cases 10–14).

TABLE 2. CONTROL DATA

Spatial frequency (c/deg)	Zero eccentricity (n = 10)	3.75° eccentricity (n = 10)				7.5° eccentricity (n = 10)				Combined results (n = 40)	
		Nasal	Temporal	Superior	Inferior	Nasal	Temporal	Superior	Inferior	3.75° eccentricity	7.5° eccentricity
0.5	37.7 (3.4)	35.2 (2.7)	35.8 (2.01)	34.38 (2.15)	33.7 (2.29)	34.3 (3.0)	32.6 (2.39)	32.5 (2.86)	33.2 (1.66)	34.8 (2.35)	33.9 (2.55)
1.0	43.0 (1.89)	39.8 (2.03)	39.8 (1.89)	38.8 (1.63)	39.3 (1.34)	37.6 (1.61)	37.7 (1.64)	36.6 (2.05)	36.5 (0.85)	39.4 (1.73)	37.1 (1.64)
2.0	44.7 (2.1)	40.9 (1.56)	40.7 (2.05)	39.1 (1.99)	38.5 (1.99)	37.3 (2.6)	37.2 (1.54)	36.2 (1.92)	36.1 (2.19)	39.8 (2.32)	36.7 (1.64)
4.0	43.5 (2.22)	38.8 (1.81)	37.3 (2.9)	36.6 (1.75)	36.1 (2.09)	33.4 (2.63)	32.3 (3.0)	31.8 (1.94)	31.6 (2.18)	37.2 (2.33)	32.3 (2.47)
8.0	38.4 (5.17)	27.6 (4.13)	27.1 (3.5)	26.8 (3.76)	25.7 (5.2)	12.8 (3.3)	14.9 (4.76)	11.7 (3.56)	12.1 (4.4)	26.8 (4.1)	13.6 (4.36)
16.0	29.5 (5.63)	9.8 (3.74)	9.9 (5.57)	7.8 (4.7)	7.8 (4.6)	—	—	—	—	8.8 (4.6)	—
Acuity (c/deg)	43.8 (10.7)	20.6 (2.4)	20.8 (3.2)	19.8 (2.48)	19.7 (2.76)	11.5 (0.86)	11.7 (2.06)	11.1 (1.21)	11.3 (1.54)	20.2 (2.67)	11.4 (1.44)

Data for the 10 control subjects. Mean threshold contrast sensitivity results are shown together with, in parentheses, the standard deviations of the means. The values given are dB where dB = 20 log (contrast sensitivity). A dB represents a ratio and sensitivities are given in relation to 100% contrast: 40 dB represents a contrast sensitivity of 100, 20 dB a contrast sensitivity of 10 and so on. For each subject, and at each eccentricity, grating acuity was predicted by a method described in fig. 3

RESULTS

Control Data

The results obtained in the control group are in close agreement with previous studies of contrast sensitivity across the visual field (*see*, e.g., Robson and Graham, 1981; Regan and Beverley, 1983; Wright and Johnston, 1983). Contrast sensitivity is maximal at the fovea for all spatial frequencies used in this investigation. Contrast sensitivity falls off, to a first approximation, monotonically at increasing eccentricities. The slope of the function relating contrast sensitivity to angular eccentricity depends upon the spatial frequency of the stimulus, being increasingly shallow at lower spatial frequencies. If contrast sensitivity is plotted against eccentricity expressed as the number of grating periods, then the slope is the same for all spatial frequencies (Robson and Graham, 1981). The slope is unaffected by the temporal frequency of modulation of the stimulus within the spatial frequency range employed in the present investigation (Wright and Johnston, 1983).

A number of investigators have reported that the fall-off in contrast sensitivity and acuity with eccentricity differs along the horizontal and vertical meridians. Rijsdijk *et al.* (1980) found, in a single subject, elliptical isocontrast sensitivity loci, the long axes of the ellipses being on the horizontal meridian. Regan and Beverley (1983) found the same relationship in one subject, but in another contrast sensitivity fell off more steeply with horizontal than with vertical eccentricity. In our 10 subjects the mean results indicate slightly higher sensitivities on the horizontal than the

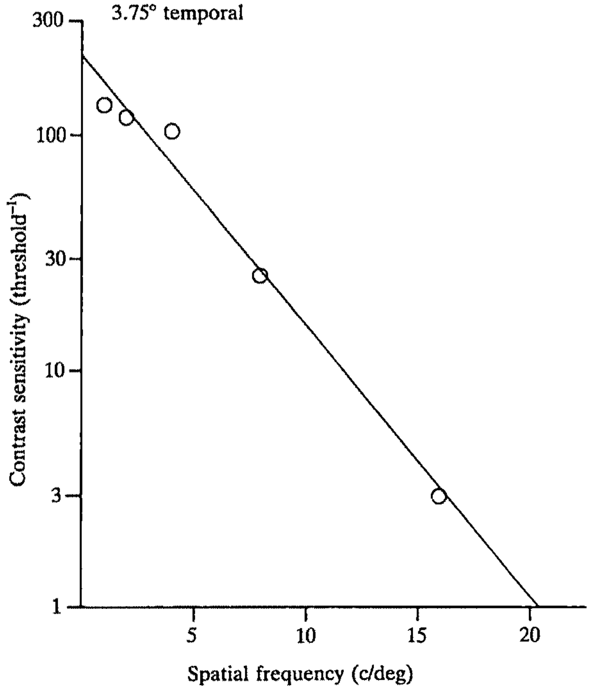

FIG. 3. In this study spatial acuity was calculated by extrapolating the high frequency limb of the contrast sensitivity functions to 100% contrast. As the fall-off in sensitivity is exponential there is a straight line relationship between log contrast sensitivity and linear spatial frequency. A regression line can thus be fitted by the method of least squares and the intercept on the X axis taken to be the spatial resolution limit. $r = 0.9922$, acuity = 20.8 c/deg.

vertical meridians. The effect is a small one, however, and in subsequent analyses it was considered justified to combine the results obtained at each eccentricity (*see* Table 2).

The acuity values shown in Table 2, and in data obtained from the patient population, were estimated by extrapolating the high frequency limb of the contrast sensitivity function to 100% contrast (*see* fig. 3 for explanation).

Results Obtained in Cases of Optic Neuritis

Figs 4, 5, and 6 show examples of the results obtained at zero, 3.75 and 7.5° eccentricity in the affected eyes of 3 patients with unilateral optic neuritis. The clinical details of these patients are shown in Table 1. In the lower panels of these figures contrast sensitivity (on the vertical axes) is plotted against spatial frequency (on the horizontal axes). The contrast sensitivity functions have also been plotted as visuograms in the upper panels of figs 4, 5 and 6. The difference between the logarithm of the patient's threshold contrast and the mean log threshold contrast obtained in the control group is plotted (in log units on the vertical axes) against spatial frequency (on the horizontal axes). This is equivalent to plotting the log ratios of the two contrast values. The visuogram, so named by analogy with the more familiar audiogram, was first introduced by Bodis-Wollner and Diamond (1976) and gives a quantitative estimation of contrast threshold elevation (contrast sensitivity loss).

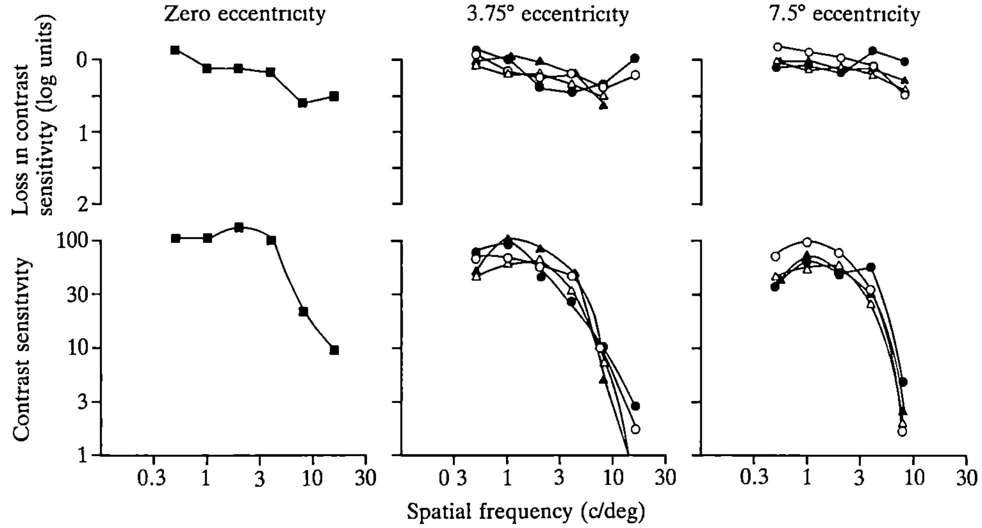

FIG. 4. In the lower panels contrast sensitivity (on the vertical axes) is plotted against spatial frequency (on the horizontal axes) In the upper panels the same results are plotted in the form of visuograms, the contrast sensitivity loss being the difference (in log units) between the log threshold contrast of the patient and the mean control log threshold contrast at the same spatial frequency. Results are shown for *Case 9* (*see* Table 1 for clinical details) Contrast sensitivity functions are shown for 9 positions in the visual field at eccentricities of zero, 3.75 and 7.5° (*see* fig. 2) The four symbols in the centre and right-hand upper and lower panels correspond to nasal (●), temporal (○), superior (▲) and inferior (△) loci. If a symbol is not plotted for a given spatial frequency then that spatial frequency is beyond the acuity limit for that patient (i.e., was not seen at 100% contrast).

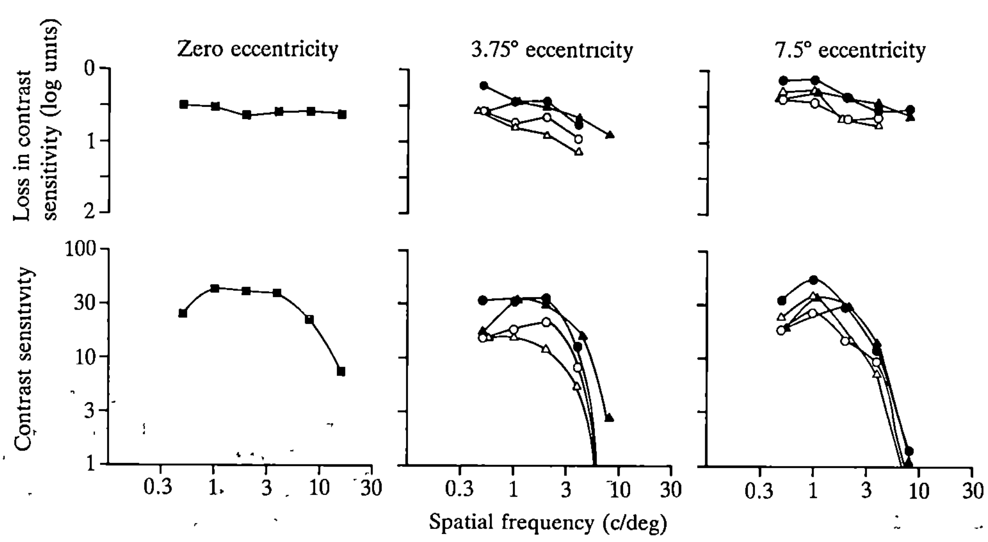

FIG. 5. Contrast sensitivity functions determined at 9 visual field locations and corresponding visuograms are shown for *Case 5*. *See* legend to fig. 4 for explanation.

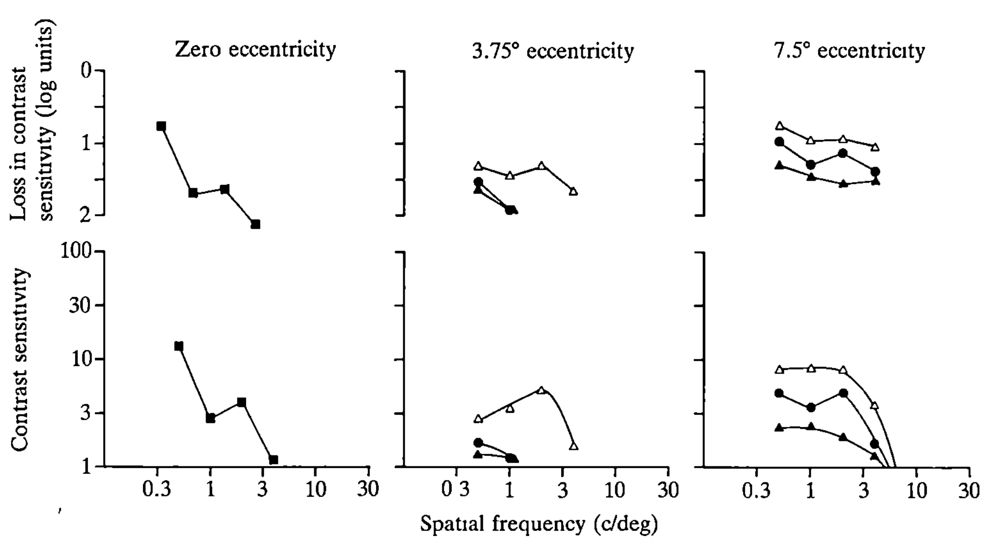

FIG. 6. Contrast sensitivity functions and visuograms are shown for *Case 1*. *See* legend to fig. 4 for explanation. It was found that in patients with a larger overall deficit there was a tendency for there to be a greater variation in the contrast sensitivity loss at different positions in the visual field. The results shown in figs 4, 5, and 6 exemplify this. Case 1 was found to have a centrocaecal scotoma on visual field testing (*see* fig. 7).

In the left hand panels of figs 4, 5 and 6, the results obtained at zero eccentricity are plotted. The centre and right hand panels show the results obtained at eccentricities of 3.75 and 7.5°, and the four symbols refer to nasal, temporal, superior and inferior visual field locations (*see* fig. 2 and legend to fig. 4). If a symbol is not plotted at a given spatial frequency then that stimulus was not seen even when presented at maximum (100%) contrast; in other words, that spatial frequency was beyond the patient's acuity limit.

In general terms it was found that the more severe was the overall deficit the more heterogeneous was the loss of contrast sensitivity within the central field: these 3 patients (figs 4, 5, 6) exemplify this. The magnitude and in some cases the general form of the contrast threshold elevation varied with visual field location. The central fields of Cases 9 and 5 were full to a 5/2000 target using the Bjerrum screen. It remains possible that a more detailed examination of the visual field, for example with coloured targets, may have revealed relative field defects. Case 1 was found to have a centrocaecal scotoma and his visual field loss, shown in fig. 7, may be compared with the regional contrast sensitivity losses shown in fig. 6. As can be seen in the visuograms of these 3 cases (upper panels of figs 4, 5 and 6) the magnitude of the contrast threshold elevation frequently varied with spatial frequency, although the nature of the spatial frequency dependence of the loss differed (*see* below), even at different visual field locations in one individual.

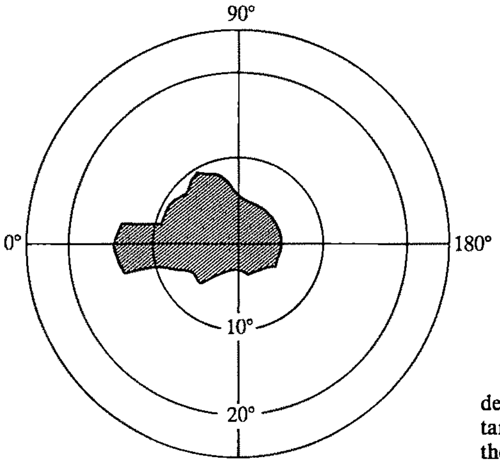

FIG. 7. Visual field of *Case 1* who is one of the patients who demonstrated a scotoma when tested with a 5/2000 white target on a Bjerrum screen. This result may be compared with the loss in regional contrast sensitivity shown in fig. 6.

In fig. 8 the results shown in figs 5 and 6 are replotted. In the normal subject contrast sensitivity is highest at the fovea for all spatial frequencies employed in this study (*see* Table 1). This situation can be modified in a highly complex manner in optic neuritis. The filled squares show the contrast sensitivity functions obtained using central fixation for Cases 5 (upper panel) and 1 (lower panel). It can be seen that for Case 5 the fovea is more sensitive only at higher spatial frequencies whereas for Case 1, central vision is more sensitive only at the lowest spatial frequency. The perceptual consequences of these effects are unknown. There are important theoretical considerations regarding the use of large areas of grating to study the visual loss in a condition which affects the visual field in a patchy manner (*see* Discussion).

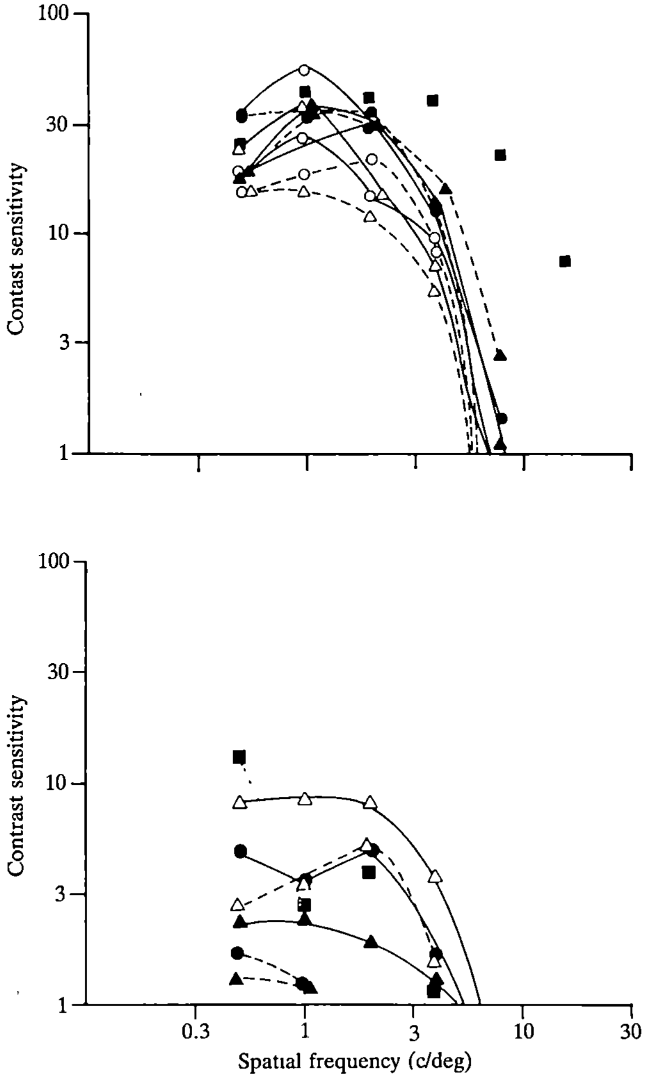

FIG. 8. The contrast sensitivity functions measured at the 9 visual field locations for *Case 5* (*upper panel*) and *Case 1* (*lower panel*) are shown replotted from figs 5 and 6. *See* legend to fig. 4 for an explanation of the symbols. The aim of this figure is to illustrate that contrast sensitivity measured using larger areas of grating will show the upper 'envelope' of the complex pattern of visual loss shown here. In a normal subject thresholds will be determined by sensitivity at the fovea which is higher than sensitivity in the periphery for all spatial frequencies (*see* Table 1) In cases of optic neuritis with patchy involvement of the visual field this is not necessarily the case and, indeed, different regions of the field may determine sensitivity for different spatial frequencies.

The 82 visuograms obtained in this study were analysed according to the spatial frequency dependence of the threshold deficit. In 65 (79.3%) the loss increased with increasing spatial frequency. With few exceptions the relationship with spatial frequency was monotonic (zero eccentricity in Case 1, shown in fig. 6, is one example of a nonmonotonic increase). In 11 (13.3%) the loss was unaffected by spatial

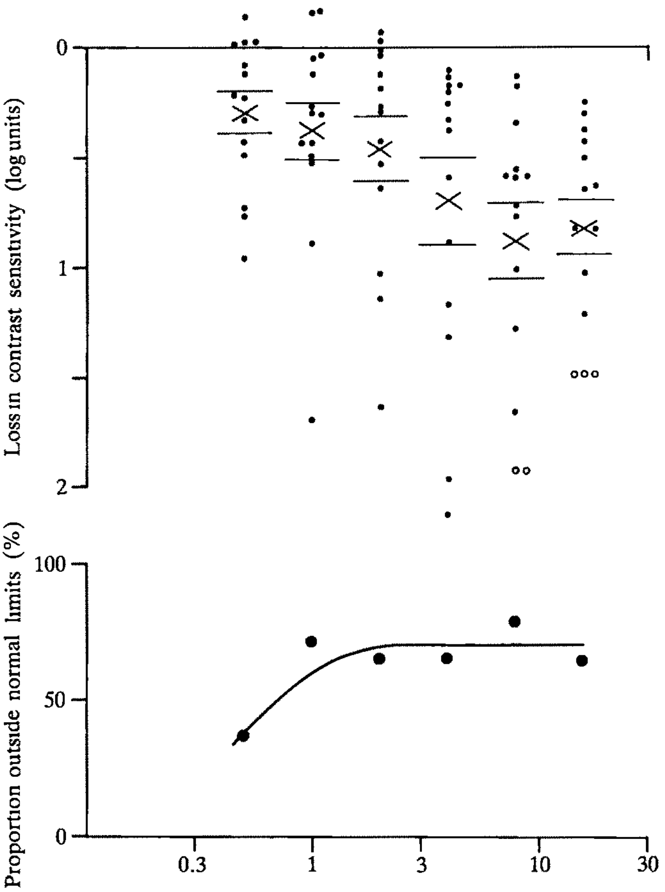

FIG. 9. In the *upper panel*, contrast sensitivity loss (threshold contrast elevation) in log units is plotted against spatial frequency for 14 cases of optic neuritis. The stimulus subtended 2.5° in diameter and was viewed centrally (*see* fig. 2). The contrast sensitivity loss is the ratio of the value obtained in each patient to the mean value obtained in the control group (i.e., the difference between the logarithms of the patient and control threshold contrasts). This ratio is shown in log units on the vertical axis and the data are shown as filled circles in the upper panel. In some instances the stimulus was not seen even at 100% contrast (i.e., the stimulus was beyond the spatial acuity limit); these data have been plotted as open circles. The mean loss in contrast sensitivity at each spatial frequency is indicated by the crosses and the SEMs by the horizontal lines. In the *lower panel* the same data have been plotted in a different way The proportion of contrast sensitivity results obtained in the patients which fell below the 95% (-2 SD) confidence limits derived from the control population has been plotted against spatial frequency. In both cases the loss in contrast sensitivity is greater at higher than lower spatial frequencies. The effect of spatial frequency on the loss in contrast sensitivity shown in the upper panel is statistically significant (method of least squares: $P < 0.001$; $r = 0.43$; $df = 98$).

frequency (did not differ by more than 3 dB at any spatial frequency tested) and in the remaining 6 (7.3%) the loss was maximal at an intermediate spatial frequency. In no case was the loss maximal at low spatial frequencies. In any individual patient more than one pattern of loss might occur at different eccentricities (*see*, e.g., the results for Case 5 in fig. 5; at zero eccentricity the visuogram shows a threshold

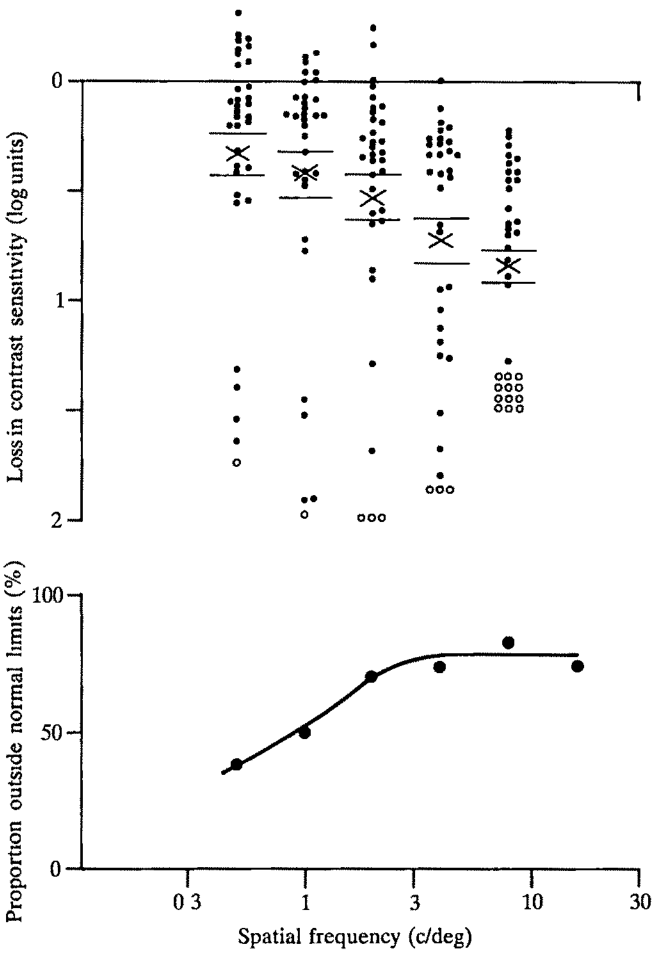

FIG. 10. Results are shown for 34 retinal positions in 9 cases of optic neuritis at an eccentricity of 3.75°. In the *upper panel* loss in contrast sensitivity in log units (on the vertical axis) is plotted against spatial frequency In the *lower panel* the proportion of results falling outside the 95% confidence limits derived from the control population is plotted against spatial frequency. The legend to fig. 9 gives a detailed explanation of the symbols. The effect of spatial frequency on the loss in contrast sensitivity at this eccentricity (*upper panel*) is statistically significant ($P < 0.001$; $r = 0.33$; df = 168).

elevation of 0.5 log units at all spatial frequencies, whereas at all other eccentricities the loss increased at higher spatial frequencies).

In order to determine whether there was an increased likelihood for sensitivity to any particular group of spatial frequencies to be affected following an attack of optic neuritis, the effect of spatial frequency on the group results was determined. The contrast sensitivity losses at zero, 3.75 and 7.5° eccentricities for all patients are plotted against spatial frequency in figs 9, 10 and 11, respectively. The results have been analysed in two ways. In the upper panels the contrast sensitivity losses have been plotted as visuograms. Individual data points are shown, as well as the means

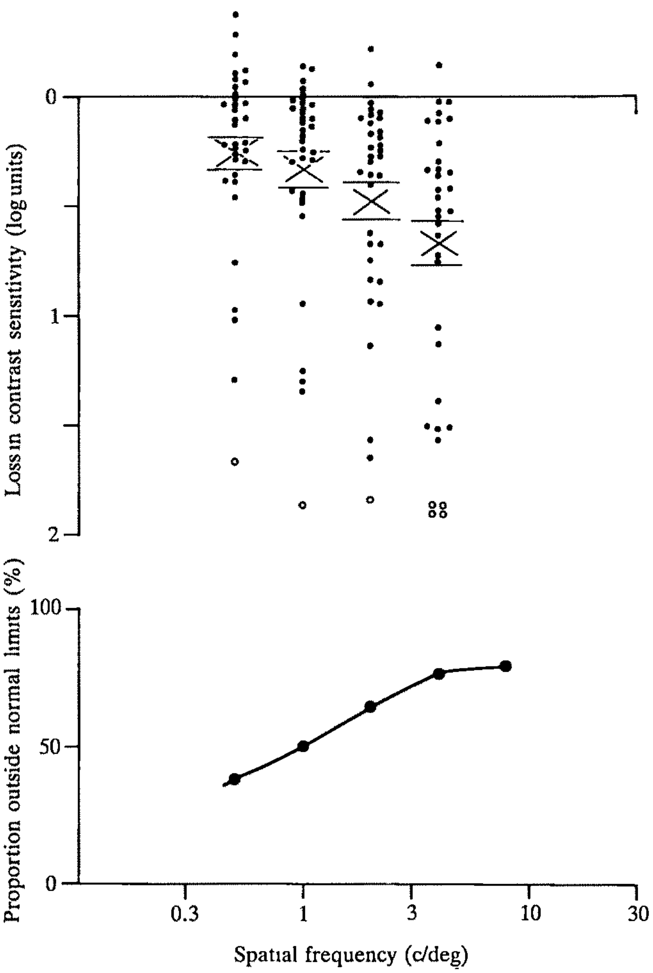

FIG. 11 Results are shown for 34 retinal positions in 9 cases of optic neuritis at an eccentricity of 7.5°. In the *upper panel*, loss in contrast sensitivity in log units (on the vertical axis) is plotted against spatial frequency. In the *lower panel* the proportion of results falling outside the 95% confidence limits derived from the control population is plotted against spatial frequency. The legend to fig. 9 gives a detailed explanation of the symbols. The effect of spatial frequency on the loss in contrast sensitivity at this eccentricity (*upper panel*) is statistically significant ($P < 0.001$; $r = 0.30$; df = 134).

and SEMs at each spatial frequency. In the lower panels the proportion of the thresholds obtained in the optic neuritis eyes falling below the 95th centile of the control contrast sensitivity results is plotted against spatial frequency.

The reason for plotting the results in the two formats shown in figs 9, 10 and 11 is that neither of the scales is uniform across spatial frequency. For example, for 2 c/deg the mean control contrast sensitivity at 3.75° eccentricity was 100, whereas for 16 c/deg the mean contrast sensitivity was 3.1. Thus the maximum possible contrast sensitivity loss (which occurs if the grating is not seen at a contrast level of

100%) is 2 log units whereas at 16 c/deg it is only 0.5 log units. The results obtained at the highest spatial frequencies have therefore been omitted from the upper panels of these figures. A different problem arises when the results are plotted as the proportion falling below the 95th centile (lower panels of figs 9, 10, 11). The SDs of the control data vary with spatial frequency and are greater at higher spatial frequencies (*see* Table 2). Hence contrast sensitivity losses need to be greater before they will fall below the 95th centile at the higher than at the lower spatial frequencies. Nevertheless these results have been included because it was possible to plot the results obtained at the highest spatial frequencies at each eccentricity, whereas these results would be difficult to interpret in the visuograms and have been omitted.

It should be noted that both of these scale compression effects will tend to diminish the magnitude of the overall contrast sensitivity loss at the highest spatial frequencies. Despite this it can be seen in figs 9, 10 and 11 that there was a trend for the group threshold deficit to increase at higher spatial frequencies as was antici-

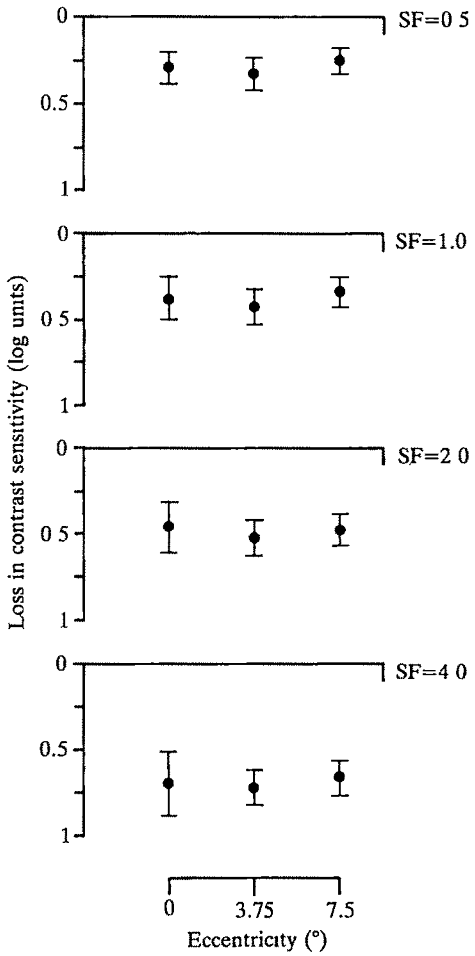

FIG. 12. The mean loss in contrast sensitivity found in the cases of optic neuritis is plotted against eccentricity Results are shown for four spatial frequencies. The error bars show the SEMs. There is no effect of eccentricity on the contrast sensitivity loss within the central 10° examined in this group of patients.

pated from the individual results. Regression analysis by the method of least squares was carried out on the data plotted in the visuograms (upper panels of figs 9, 10, 11). The effect of spatial frequency on the mean contrast sensitivity loss in this group of patients was found to be statistically significant at all three eccentricities: for zero eccentricity $P < 0.001$ ($r = 0.43$; $df = 98$); for 3.75° eccentricity $P < 0.001$ ($r = 0.33$; $df = 168$); and for 7.5° eccentricity $P < 0.001$ ($r = 0.30$; $df = 134$).

As explained above the results obtained at the highest spatial frequencies, close to the spatial acuity limits at eccentricities of 3.75 and 7.5°, would have been misleading if included in the visuogram plots in the upper panels of figs 9, 10 and 11. The results shown in the lower panels indicate that the effect of spatial frequency on the contrast threshold elevation indicated in the visuograms also applied to these high spatial frequency results.

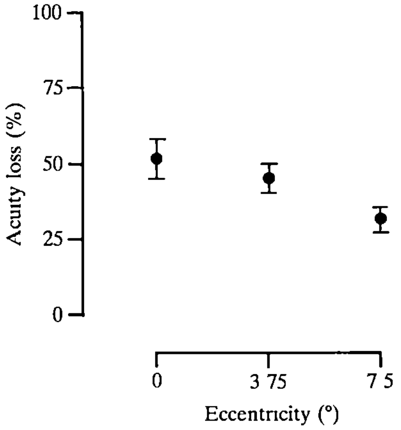

FIG. 13. Spatial acuity was estimated from the contrast sensitivity functions obtained at each eccentricity in the patients with optic neuritis by the method illustrated in fig. 3. This result was then expressed as a percentage of the mean acuity result derived from the control population (*see* Table 2). The mean percentages are plotted above against eccentricity for all the patients. The acuity loss at 7.5° eccentricity was lower than the mean percentage loss at zero eccentricity ($t = 2.235$; $df = 46$; $P < 0.05$) and at 3.75° eccentricity ($t = 2.337$; $df = 66$; $P < 0.05$).

As also stated above, and as expected from the heterogeneous manner in which the visual field is almost invariably affected in optic neuritis, in individual cases the loss of contrast sensitivity might be greatest at any of the three eccentricities tested (*see* figs 4, 5, 6, for examples). In order to determine whether sensitivity was more likely to be impaired at any particular eccentricity the mean results obtained in the entire patient group were analysed. The mean loss of contrast sensitivity obtained in the optic neuritis cases is plotted against eccentricity in fig. 12 for 0.5, 1, 2 and 4 c/deg. There was no significant effect of eccentricity on the reduction in mean contrast sensitivity at any of these spatial frequencies. In view of the fact that results at the higher spatial frequencies were not obtainable at all eccentricities and because of the scale compression effects described above, the results at high spatial frequency have been analysed by plotting reduction in grating acuity against eccentricity. Grating acuity was estimated by the extrapolation method described in fig. 3. For each subject the spatial acuity result was divided by the mean of the control results (*see* Table 2) and the result expressed as a percentage. The mean percentage acuity reduction at each of the three eccentricities was then calculated and the results with the SEMs are shown in fig. 13. There was no significant difference between the results obtained at zero and 3.75° eccentricity for the group as a whole. The percentage acuity reduction at 7.5° eccentricity, however, was significantly less than both the result obtained at zero eccentricity ($t = 2.235$; $df = 46$; $P < 0.05$) and the result obtained at 3.75° eccentricity ($t = 2.337$; $df = 66$; $P < 0.05$).

DISCUSSION

The results of this investigation permit us to address three questions. (1) Is there any particular eccentricity within the central 10° which is more likely to be affected following an attack of optic neuritis? (2) How variable is the contrast sensitivity loss at different locations in the central field in individual patients and what are the implications of these local losses for contrast sensitivity measurement using larger areas of grating? (3) Are any particular spatial frequencies more likely to be affected in optic neuritis, in other words is there, overall, a spatial frequency dependence of the visual loss?

The first two questions could be answered by conventional perimetry and previous work is reviewed below. An advantage of the contrast sensitivity technique is that it provides a *quantitative measure* of the visual loss. Such a quantitative comparison is difficult to derive from isopter perimetry although 'profile perimetry', where luminance increment thresholds are measured (*see*, e.g., Harms, 1976) could be used in a similar manner. The third question could not be answered by any conventional perimetric technique. Isopter perimetry, like many standard tests of visual function, is concerned solely with the acuity limit of vision (highest detectable spatial frequency). The measurement of luminance increment thresholds across the visual field using spots of different sizes is inappropriate because spots are poorly localized in spatial frequency; in other words, they contain many different spatial frequencies. Furthermore, as discussed in the Introduction and elsewhere (Hess and Plant, 1986), the results of measurements of spatial contrast sensitivity using relatively large areas of grating, centrally fixated, are ambiguous because losses specific for retinal loci may account for a spatial frequency-dependent loss in contrast sensitivity or, at least, both may occur. In most previous studies, field sizes of up to 10° in diameter have been employed, although for technical reasons smaller field sizes have been used when studying higher spatial frequencies. As illustrated in fig. 8, sensitivity to a large area of grating will be determined by the upper envelope of the kind of local losses shown in figs 4, 5 and 6.

Is the Central Foveal Projection ('Papillomacular Bundle') Peculiarly Vulnerable in Optic Nerve Demyelination from Optic Neuritis and Multiple Sclerosis?

The view has been expressed by various authors from time to time that the axons of ganglion cells subserving the central, foveal visual field are particularly likely to be affected in optic neuritis and MS (*see*, e.g., Brain, 1977; Glaser, 1978). The central projection is often referred to as the papillomacular bundle in primates. The papillomacular bundle was originally described in postmortem studies of cases of tobacco/alcohol amblyopia which were found in life to have centrocaecal scotomata (Wilbrand and Sänger, 1904) and thus, properly speaking, includes the projection of the retinal region between the fovea and the disc as well as that of the fovea itself. In this discussion the use of the term 'foveal projection' is preferred.

The optic nerve fibres subserving the central few degrees differ in certain respects from other ganglion cell axons, particularly with respect to fibre diameter. That the central retinal projection contains a higher proportion of small diameter fibres has been inferred from the measurement of conduction velocity in the cat (Stone and Freeman, 1971) and the primate (Ogden and Miller, 1966). Potts *et al.* (1972) determined the proportion of small fibres which were lost following a central retinal lesion in the monkey and came to a similar conclusion. The lesions made by Potts *et al.* (1972) were larger than the fovea and the most accurate estimate of fibre diameters in the foveal and arcuate projections has been provided by Ogden (1984), who has determined by electron microscopy axonal diameters in intraretinal nerve fibre bundles in the monkey. The mean diameter in 44 papillomacular bundles was 0.4 μm and in 38 arcuate bundles 0.6 μm. The lower range of fibre size (0.1 μm) was present in all fibre groups but the papillomacular bundles lacked fibres larger than about 2.5 μm.

The higher proportion of small diameter fibres may explain the undoubted vulnerability of the central field projection in tobacco amblyopia and certain other toxic disorders if these are more susceptible to the effects of the toxins (Nettleship and Edmunds, 1881; Traquair, 1928; Foulds, 1981). It is not the only possible explanation, however. Differences in fibre density, the anatomical position of the papillomacular bundle in the nerve and its blood supply, the blood supply of the relevant retinal region, or other, unknown, factors may be important.

The foveal projection is made up of axons of the ganglion cells of the nasal and temporal hemifoveae which take, respectively, direct and curvilinear courses to the optic disc. The fibres concerned therefore subserve the central few degrees of the visual field (Polyak, 1957; Ogden, 1984). The human fovea is likely to be slightly larger than that of the monkey (Polyak, 1957; V. H. Perry, personal communication) and the pericentral portion of the typical scotoma in tobacco and other toxic amblyopias is most frequently limited to the central 5° (Nettleship and Edmunds, 1881; Traquair, 1948; Foulds, 1981), although many exceptions to this occur. Hence if it was the case that the central foveal projection was more likely to become demyelinated than other parts of the optic nerve, or that its fibres were more likely to be functionally impaired by demyelination, then we would expect to see an overall greater reduction in contrast sensitivity in the central 5° than in the region between 5 and 10°. In view of the patchy nature of the visual field involvement in optic neuritis, only in the pooled data from a large sample could such an effect be demonstrated. The results shown in fig. 12 indicate that in this group of patients there was no increased susceptibility of the central foveal projection as far as luminance contrast sensitivity is concerned for low and intermediate spatial frequencies. The extrapolated acuity data permit the additional analysis of results obtained at the highest spatial frequencies at each retinal location which could not be included in fig. 12. For spatial acuity there was less reduction at 7.5° eccentricity than at either eccentricity within the central 5° (fig. 13). This was, however, a small difference, statistically significant at the 5% level.

Previous studies which have employed conventional perimetry have not indicated any preferential impairment of the central 5° of the visual field. In acute optic neuritis the central field may be more commonly affected; Traquair (1948) pointed out that the most characteristic field defect in acute optic neuritis is central and 10 to 20° in diameter, but by no means always pericentral. The impairment of optic nerve function in acute optic neuritis is likely to be multifactorial. Halliday and McDonald (1977) have argued that the rapidity of visual recovery following acute optic neuritis suggests that the visual loss may in part be due to optic nerve oedema rather than the primary pathological process. It is only in the study of a large group of patients at follow-up that any confident statement regarding the vulnerability of any portion of the field to the primary disease process can be made. The idea that a central scotoma is the 'rule' in optic neuritis led Bradley and Whitty (1967) to exclude cases with other field defects from their series. They found no difference in the subsequent clinical course of cases with 'atypical' field losses.

Traquair did not publish visual fields at follow-up in optic neuritis in detail, although he commented that from his experience of the disorder he did not consider the macular projection to be peculiarly vulnerable (Traquair, 1925). Wybar (1952) examined 33 cases of MS and found central defects in 21.2%, paracentral in 12.1% and peripheral in 39.4%. Hyllested and Møller (1961) found approximately equal numbers of peripheral and central/paracentral defects in cases found to have abnormal fields on follow-up. Both the studies of Nikoskelainen (1975) and of Perkin and Rose (1979) found equal numbers of cases having central defects and paracentral/peripheral defects. In the large series of 120 cases reported by Perkin and Rose (1979) no patients showed a defect limited to the central 5° at follow-up and peripheral extension was found in most of the cases with central defects. An equal number of cases showed sparing of the central 5–10° and in 39% patchy depression of the field between 5 and 10° was found with preservation of the central field and acuity.

Citing also the earlier studies of Klingman (1910) and Frisén and Hoyt (1974), Perkin and Rose concluded that arcuate fibres are more likely to 'degenerate' after demyelination than fibres in the foveal projection. Patterson and Heron (1980) examined the visual fields of 55 cases of MS or previous optic neuritis; 96% were found to have scotomata, almost all of which were outside the central 20°. In 76% of cases the scotomata were arcuate. These results confirmed the assertion of Perkin and Rose quoted above but the authors pointed out that, as demyelination can block conduction without causing axonal loss, arcuate defects would be expected to be more prevalent than nerve fibre bundle defects observed ophthalmoscopically. That focal lesions of the optic nerve (as opposed to retinal nerve fibre bundle defects) can give rise to arcuate scotomata is known from the anatomical studies of Hoyt (1962).

From previous visual field studies, then, it seems that there is no more likelihood for the central 5° of the visual field to be affected than any other part of the field following an attack of optic neuritis. The present investigation has permitted a quantitative confirmation of this conclusion: the mean contrast sensitivity loss in this group was constant with eccentricity—at least for luminance vision and for spatial frequencies from 0.5 to 4 c/deg. There was, however, a small difference in the case of spatial acuity which was less affected in the paracentral region. This result was to be expected in view of the finding that the deficit tends to be greater at higher spatial frequencies, as acuity is higher in the central than the paracentral field.

How Patchy is the Contrast Sensitivity Loss within the Central Visual Field in Optic Neuritis?

Our results suggest that there are differences in the magnitude of the spatial contrast sensitivity loss at different regions within the central field in most of our cases as was to be expected from what is known of the uneven manner in which the visual field is affected. The results obtained in the 3 cases shown in figs 4, 5 and 6 exemplify this and also the observation that the patchy nature of the loss became more obvious in cases having larger overall deficits. Our results indicate a novel aspect of this variability. The spatial frequency dependence of the visual loss may also vary from one retinal region to another in a single case. This can be seen in the individual results shown in figs 4, 5 and 6. For example, Case 5 was found to have a contrast sensitivity loss which did not vary with spatial frequency at zero eccentricity but which increased at higher spatial frequencies at all other tested visual field locations.

Harms (1976) reported measurements of luminance increment threshold in a case of retrobulbar neuritis in the recovery phase. Within areas of the visual field in which sensitivity was reduced, marked scattering (point-to-point variation) of the thresholds was found. It is not clear whether the precise retinotopic distribution of the scattering was repeatable—that is, whether it represented genuine local variability or variability in the threshold measurement in time (that the latter may occur was suggested by Patterson *et al.*, 1980). Nevertheless, the possibility that marked local variation in the deficit within relatively large areas of depressed visual field might occur was shown by Harms. Snelgar *et al.* (1985) examined a variety of visual functions at multiple retinal sites in cases of suspected and known MS. They found no increased interquadrant variation for any parameter in the patient group when compared with a control population. This result is not necessarily at variance with our own. Their clinical group was selected to have mild visual impairment (all were 6/9 or better and performed normally on the City University Colour Vision Test) and, as stated above, we found the variability to be more marked in cases with a greater overall deficit.

The patchy nature of the contrast sensitivity loss has important consequences for the interpretation of results obtained using relatively large areas of grating. If it is assumed that detection of a large area of grating will be determined by that part of the field which is most sensitive at any given spatial frequency, then it follows from the results shown in fig. 8 that the upper envelope of such groups of contrast sensitivity functions will determine the shape of the large field result.

Is the Contrast Sensitivity Loss in Optic Neuritis Dependent on Spatial Frequency?

Our results confirm previous studies (*see* Introduction) in showing that there is more than one way in which the loss in contrast sensitivity in optic neuritis may vary with spatial frequency. This has been found even when the confounding influence of the distribution of the anomaly across the visual field is minimized by the use of small patches of grating and by examining peripheral retinal regions. Occasionally a loss that is greater at intermediate than at higher or lower spatial frequencies is seen, as is a loss that is independent of spatial frequency. In our study, however, 79% of the sample showed a loss that was maximal at high spatial frequencies. There was no instance of a loss greater at lower spatial frequencies. This is reflected in the combined results (figs 9, 10 and 11) which show a statistically significant effect of spatial frequency on the threshold deficit ($P < 0.001$ for all three eccentricities). The difference in the mean loss at the lowest and highest spatial frequencies was around 0.5–0.75 log units (i.e., the threshold elevation was, on average, greater by a factor of between 3.0 and 5.5). Although not an invariable finding this was overall the most common pattern of loss in this group of patients.

The fact that deficits in contrast sensitivity can be dependent on spatial frequency (and, indeed, usually are) when small eccentric patches of visual field are examined, is of interest. Although uncommon, a loss which is maximal at an intermediate spatial frequency can also be seen under these conditions. Such a relationship of the loss to spatial frequency is shown, for example, in the results for Case 9 (fig. 4, 3.75° nasal). It is more difficult to account for these observations on the basis of the distribution of the anomaly across the visual field than on results obtained with larger areas of grating centrally fixated because the change in the spatial frequency dependence of sensitivity with eccentricity is more gradual at eccentricities away from the fovea. Our findings support the suggestion that neural mechanisms responsible for the detection of different spatial frequencies *can* be impaired differentially in optic neuritis at a given retinal location, as was originally suggested by Regan *et al.* (1977). In a recent study, Regan and Maxner (1986) reached a similar conclusion. Furthermore we have shown that although there is no unitary pattern of loss, overall the most common finding is that the lower spatial frequencies are less affected.

It was considered necessary to keep the stimulus area small and constant to fulfil the overall aims of this study. As a consequence of this, as spatial frequency has been reduced, the spatial frequency content of the stimulus has become broader. It is generally thought that the effect of this is most pronounced when there are less than 5 complete cycles of the grating present (Howell and Hess, 1978) which in our experiments was the case for the spatial frequencies lower than 2 c/deg. It is, however, difficult to predict the consequences of broadening the spatial frequency content of the stimulus at lower spatial frequencies as the bandwidth of the neural detectors concerned is not known. It is possible to say that it is unlikely that the tendency for the higher spatial frequencies to be more affected in the present data is an artefactual consequence of the change in the number of bars in the gratings. The function relating contrast sensitivity to grating area asymptotes above 5 cycles in width and height (Howell and Hess, 1978). If it were the case that the effect of optic neuritis were to reduce the effective area of the grating by the same amount whatever the spatial frequency, then sensitivity would be *less* impaired at the higher spatial frequencies.

This result is similar to the effect of spatial frequency on the latency of the visual evoked potential (VEP) in optic neuritis. Overall the delay in the transient VEP was found to increase at higher stimulus spatial frequencies in a group of recovered optic neuritis cases (Plant, 1983). It is likely that contrast sensitivity deficits and changes in VEP latency reflect different aspects of the impairment of optic nerve function in optic neuritis as the two measurements are not well correlated in the disorder, whereas VEP amplitude and contrast sensitivity deficits show a significant correlation (Bodis-Wollner *et al.*, 1979; Plant, 1983; Harding and Wright, 1986; Plant and Hess, 1986).

It is also evident that both for VEP delays and contrast sensitivity deficits the extent to which the abnormality is dependent upon spatial frequency in individual cases varies. To this extent the findings also resemble other instances of selective impairment of visual function in optic neuritis such as the relatively greater impairment of the 'sustained' temporal channel (Plant and Hess, 1985) and the greater impairment of chromatic than luminance sensitivity (Mullen and Plant, 1986). In each of these studies the effect reported was not demonstrated in every case and showed considerable variability in its magnitude between individual cases. Instead, if a consistent pattern does emerge, it is in certain possible types of loss that do not occur. In no case in the present study was the abnormality, as quantified by measuring contrast sensitivity, found to be maximal at low spatial frequencies, and this is also true for the VEP delay (Plant, 1983). In no case was the 'transient' temporal channel found to be more impaired than the 'sustained' channel (Plant and Hess, 1985) or luminance vision to be significantly more impaired than colour vision (Mullen and Plant, 1986). Using different stimulus conditions, other workers have found luminance and chromatic mechanisms to be equally affected in cases of MS (Foster *et al.*, 1986; *see also* Foster, 1986, for a review article). These results do not necessarily conflict with the findings of Mullen and Plant (1986) who found *some* individuals with equal loss to colour and luminance; differences in the patient groups may account for the discrepancy. The other major difference between the two studies was field size, which was large (6°) in that of Mullen and Plant (1986).

The Neural Deficit in Optic Neuritis

There are a number of significant problems in attempting to relate studies such as this to our knowledge of optic nerve physiology. The first concerns the possibility that lesions elsewhere in the visual pathway may contribute to the visual anomaly in optic neuritis. In studies of visual function in cases of advanced MS, it is very likely that plaques may be present, for example, in the posterior visual pathways. In studies, such as this, which deal primarily with isolated optic neuritis, this difficulty is minimized but not entirely eliminated, as asymptomatic plaques may be present even in such cases, some of which may involve the posterior visual pathways (Ormerod *et al.*, 1986). Furthermore an abnormality at retinal level, of uncertain origin, may occur in optic neuritis (*see* Plant *et al.*, 1986, for further discussion of this aspect).

A further difficulty is that although our knowledge of the neural mechanisms in the primate optic nerve has advanced in recent years, the neural basis of psychophysical measurements of contrast detection is still unknown. Primate neurophysiology would suggest that threshold contrast sensitivity to achromatic gratings is determined by cells in the magnocellular layers of the dorsal lateral geniculate nucleus, as these cells have higher contrast sensitivity than the parvocellular units and show no or weak colour opponency (Kaplan and Shapley, 1982; Hicks *et al.*, 1983; Derrington and Lennie, 1984). The retinal ganglion cells which have, at any particular eccentricity, the largest cell bodies, axons and dendritic fields project to the magnocellular layers. These have been called P-alpha cells by Perry *et al.* (1984). Parvocellular cells are more likely to subserve sensitivity to chromatic stimuli and acuity because they are colour opponent, and have smaller receptive fields (and hence higher acuity) than magnocellular cells at the same eccentricity (Derrington and Lennie, 1984; Derrington *et al.*, 1984). P-beta ganglion cells, which have smaller cell bodies, dendritic fields and axons than P-alpha cells at any given eccentricity, project to the parvocellular layers (Perry *et al.*, 1984).

Whilst it seems certain that the parvocellular cells subserve chromatic function, these cells may also contribute to achromatic threshold contrast sensitivity because they are more numerous than the magnocellular cells. Also, magnocellular cells can respond to spatial frequencies close to the acuity limits of parvocellular cells because of their higher sensitivity.

The results of studies such as this will become easier to interpret when the relationships between psychophysics and neurophysiology are better understood and, of equal importance, more detailed information is available regarding the pathological anatomy of demyelinating optic nerve disease.

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PHYSIOLOGICAL AND BEHAVIOURAL CONSEQUENCES OF SEIZURES INDUCED IN THE RAT BY INTRAHIPPOCAMPAL TETANUS TOXIN

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SUMMARY

Injecting tetanus toxin into rat hippocampus induces a syndrome of intermittent generalized seizures which recurs for about one month. Following remission from their seizures, the rats exhibit very persistent impairments of learning and memory. Learning was impaired on a circular platform task and a spatial reference memory task, and evoked responses from the commissural-CA3 pyramidal cell system were depressed for up to 22 weeks after injection. There was no significant loss of pyramidal neurons because antidromic responses, evoked from other parts of the commissural fibre system, were not affected by the toxin treatment. The depression of these pyramidal neurons provides a reasonable physiological explanation for the learning impairment. These results suggest that impairments of neuronal function can be significant factors in the development of interictal behavioural abnormalities.

INTRODUCTION

Injection of tetanus toxin into rat hippocampus produces an epileptic syndrome which in many respects resembles complex partial seizures in man (Mellanby *et al.*, 1977). This animal model is associated with abnormalities in behaviour, including hyperreactivity and aggression (Mellanby *et al.*, 1981), and impaired learning and memory (George and Mellanby, 1982; Mellanby *et al.*, 1982). Furthermore, it has the important advantage that its sequelae can be attributed to the epileptic syndrome directly, rather than to the side-effects of anticonvulsant therapy or to social factors which can confound clinical observations in man (Melin, 1984).

The intrahippocampal tetanus toxin syndrome is an example of chronic experimental epilepsy, in that seizures recur intermittently for several weeks after the injection, with the abnormal hippocampal electrical activity persisting 1-2 weeks longer than the motor attacks. However, the seizures eventually subside, as does the behavioural hyperreactivity. In contrast, the impairments in learning and memory are very persistent, and possibly are permanent. This is especially interesting because no overt cellular damage has been found in this model (Mellanby *et al.*, 1977; cf.

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kainic acid seizures, Kessler and Markowitsch, 1983). Thus it appears the tetanus toxin seizures may have disrupted learning by a more subtle mechanism than through the loss of neurons.

The hippocampus has often been linked with learning and memory. Thus it has been implicated in a number of behavioural tasks where learning is involved (for reviews, *see* O'Keefe and Nadel, 1978; Weiskrantz, 1982; Rawlins, 1985). It also exhibits a remarkable physiological phenomenon, long-term potentiation (LTP), which provides a model of learning (Bliss and Gardner-Medwin, 1973; Bliss and Lomo, 1973). In spite of the tantalizing similarities of LTP and memory, evidence of a direct link between the two has been slow to materialize. Barnes (1979) has demonstrated that senescent rats had impairments both of learning ability and of the more persistent (several days) components of LTP (*see* Rao *et al.*, 1984, for preliminary reports of further tests of the relationship of these phenomena).

The present study is directed to determining what changes in hippocampal function might be responsible for the learning impairment following remission from tetanus toxin seizures. We have chosen an injection site in the dorsal hippocampus as this was more accessible to subsequent physiological investigation than the ventral site more commonly used in other studies of this model (including one complementary to the present report: Brace *et al.*, 1985). The learning ability of the rats was assessed using a task new to experimental epilepsy, the circular platform task, which was devised by Barnes (1979) for her studies on ageing. Subsequently, LTP and other aspects of hippocampal neuronal function were examined in terminal experiments under anaesthesia.

MATERIAL AND METHODS

Male Sprague-Dawley rats of 280–320 g were given intrahippocampal injections of tetanus toxin ($n = 14$) or phosphate buffer ($n = 11$). During the following 5.5 weeks, video recordings were used to estimate the incidence of major motor seizures. Seven days after the last motor seizure had been observed, two behavioural tests were performed: an open field task to assess hyperreactivity, and 10 days later (7 weeks after injection), a circular platform task to assess learning ability. Finally, 16–22 weeks after injection, the physiological properties of hippocampal pyramidal neurons were examined in terminal experiments under anaesthesia.

Injection of Tetanus Toxin

The tetanus toxin (2×10^6 mouse LD50/mg) was kindly provided by Dr R. O. Thomson of the Wellcome Research Laboratories, Beckenham, Kent. It was dissolved in a 0.1 M phosphate buffer at pH 7.0, containing 0.2% gelatin, and was bioassayed by Dr J. Mellanby of the Department of Experimental Psychology, Oxford University, by the method of Mellanby *et al.* (1968).

The rats were anaesthetized with halothane in air through a face mask attached to a Kopf stereotaxic instrument; 0.4 μl of toxin (containing 4–6 mouse LD50) or buffer was injected bilaterally into the hippocampus, over a period of 1 min, from a Hamilton syringe at the coordinates 2.8 mm caudal to the bregma, 3.5 mm lateral, 3.5 mm below the cortical surface (Pellegrino *et al.*, 1979). The syringe was left in place for 5 min to reduce the risk of reflux of the liquid along the needle track. The wounds were cleaned and sutured, and the animals allowed to recover from anaesthesia.

Video Monitoring

The toxin-injected rats were marked with an indelible felt pen so that they could be distinguished by a video camera (Panasonic WV1850 extended red newvicon, with a wide-angle Fujinon CF12.5A MND2B lens) positioned 1.2 m above the cages. Recordings were made, using an NEC PVC 9507 U-matic video recorder, daily from 0200–0300 h and 1400–1500 h (near the midpoints of the dark and light cycles, 2000–0800 h and 0800–2000 h, respectively). Motor seizures were scored when the rats had forelimb myoclonus; typically, they also reared up on their hindlegs, with neck extended and ears flattened against the head. These seizures lasted 10–45 s; individual rats had no more than 2 per h recording session. Video recording was continued until no motor seizures had been observed on 7 consecutive days, and behavioural testing was started immediately afterwards.

Hyperreactivity

We repeated the 'open field' measurement described by Mellanby (Mellanby *et al.*, 1981) to test whether the change in injection site altered the behavioural syndrome. The 'open field' was a circular piece of chipboard 1 m in diameter with a clear perspex side 300 mm high. Its surface was marked with radial lines to divide it into 8 equal sectors, and with two concentric circles, 200 and 600 mm in diameter. The rats were tested between 2030 and 2230 h (i.e., during their active cycle) in a brightly-lit room, while a loud bell was rung at 15 s intervals. Each rat was placed in the centre of the field and observed for 5 min. We recorded (1) how often the rat crossed the radial lines; and (2) the inner and outer circles; (3) how long it spent grooming; and (4) how often and how long it spent rearing up on its hindlegs.

Learning Task (Circular Platform)

The learning task used was a circular platform task originally devized by Barnes (1979) for use with senescent rats. It is believed to depend on hippocampal function and thus is likely to be sensitive to any impairments associated with the experimental epileptic focus induced by tetanus toxin in the hippocampus. The animals had to learn to locate a safe dark box beneath one of 18 holes evenly spaced around the circumference of a circular platform, 1 m in diameter, in order to avoid illumination by two 500 W photoflood lights. The rats were prevented from using local cues by random rotations of the platform, and not the escape box, between trials. Each rat was tested twice daily, and spent the intervening 1 min in a holding cage. The number of holes an animal looked into before it chose the correct hole and the latency in seconds before it made that choice were recorded. Once all the animals had learned the location of the escape box (criterion: total of less than 4 errors on 2 consecutive trials), its location was rotated 120 deg and the rate of relearning was measured without interrupting the testing schedule.

Electrophysiological Experiments

Terminal physiological experiments were performed, 16–22 weeks after the injection of tetanus toxin, to investigate the commissural projection from the left hippocampus to the CA3 pyramidal cells of the right hippocampus. The rats were anaesthetized with halothane in air, exchanged at 400 ml/min across the mouth of a tracheal cannula; during the recordings anaesthesia was maintained with 1% halothane. Rectal temperature was maintained in the range 36–38° C with the aid of a d.c. heating pad built from high-wattage resistors.

The neocortex was exposed above the appropriate parts of the hippocampus, and was covered with silicone oil to prevent drying. Digitimer (Welwyn) NL05 tungsten microelectrodes were used both for recording and, cut back to 20–50 μm diameter, for stimulating. The coordinates for stimulation were 1.0 mm caudal to the bregma, 1.3 mm lateral (left) and about 3.5 mm below the cortical surface; for recording they were 2.8 mm caudal, 3.5 mm lateral (right) and about 3 mm deep (the 'focal' site, close to the injection site), and 1.8 mm caudal, 1.5 mm lateral (right) and about 2.5 mm deep (the 'extrafocal' or medial site, which would be expected to be outside the area of bulk spread from the 0.4 μl injection).

The recording electrodes were located in the CA3 pyramidal cell body layer with the help of the antidromic population spike in response to commissural stimulation, the shape of the synaptic evoked potentials and the presence of spontaneous unitary activity. A standard protocol was followed for each physiological experiment. First, the stimulating electrode was systematically lowered to provide 'stimulus profiles' for the antidromic and orthodromic population spikes in the CA3 response to 16 V stimuli (0.1 ms, tip-negative) to the commissural pathway. Secondly, stimulus-response (SR) curves were recorded for the focal and medial CA3 sites, using the optimum orthodromic stimulus site. Thirdly, LTP was examined, using a stimulus (in the range 4–13 V) which gave a postsynaptic population spike of 1–6 mV: records were taken at 1 min intervals for 1 h before and 1 h after the conditioning train of 50 pulses at 4 ms intervals, and subsequently at 1 record every 4 min for up to 4 h. All recordings and measurements were made with a Research Machines (Oxford) 380Z microcomputer equipped with a Digitimer (Welwyn) D201 ADC. Measurements made from the evoked potentials included (1) the rate of rise (V/s) of the first positive component of the evoked response, which provides an estimate of the excitatory synaptic current generated by the afferent volley; and (2) the amplitude of the negative antidromic and orthodromic population spikes (▲ and ●, respectively, on fig. 3), measured from a baseline interpolated between the adjacent positive maxima, which provide estimates of the number of pyramidal neurons discharged by the respective stimuli. In order to avoid bias, the electrodes were positioned by an experimenter who did not know the history of the rat under investigation.

Statistical Analysis

Statistical comparisons between the two experimental groups were made using the BMDP and SPSS packages at the University of London Computing Centre, with the help of Ms E. Paul of the Institute of Neurology Computing and Statistics Unit. Details of the tests used are given in the Results section below.

RESULTS

Epileptic Syndrome

The motor component of the seizures resembled earlier descriptions (Mellanby *et al.*, 1977). The principal visible signs included: behavioural arrest; facial myoclonus; forelimb myoclonus; and rearing up, with nose pointed up and ears flattened (tonic extension of back), often with a loss of posture and repeated rearing and falling. During each of our twice-daily 1 h observation periods, each rat had up to 2 motor seizures (but usually fewer), each lasting up to 45 s (but more typically about 15–20 s). The total number of seizures we observed in individual rats ranged from 1 to 11; from these observations we estimate that, on average, the rats would have experienced 81 motor seizures. Visible seizures started 7 days after injection (fig. 1). This long delay has been observed before with low doses of toxin, but its cause remains obscure. The rate of seizures reached a maximum at 10–15 days, and declined thereafter, none being observed after 31 days. Throughout the experiment, the rats were able to maintain themselves in good general condition.

Hyperreactivity

At 36–38 days after injection (7 days after the last seizure had been seen on the video recordings), the rats were placed in an open field to assess hyperreactivity. One rat froze during this test; this was the only example of a behaviour which might indicate a partial seizure. The toxin-injected rats crossed radial lines more often than the controls (medians of 66 vs 50; Mann-Whitney U test, two-tailed $P < 0.05$), crossed between the inner and outer circles more often (24 vs 7, $P < 0.01$), and reared

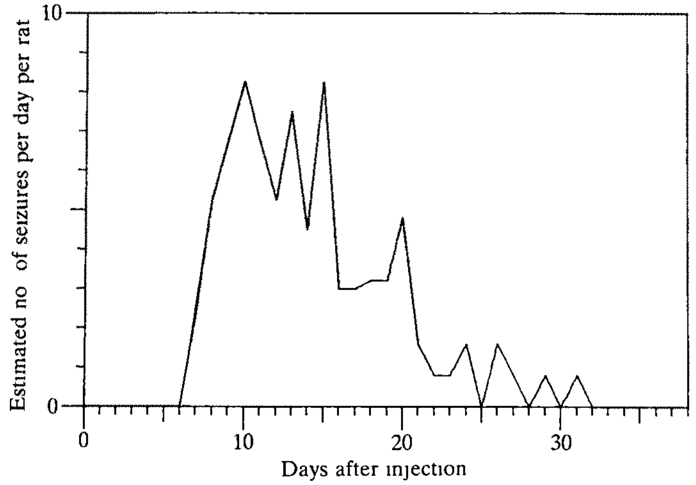

FIG 1. Mean number of visible seizures per animal per day, estimated from twice-daily 1 h video recordings, plotted against the time after injection (13 rats).

up more often (34 vs 19, $P < 0.01$). The toxin-injected rats were therefore hyperreactive compared with the controls, consistent with the observations of Mellanby *et al.* (1981) for their ventral injection site.

Learning Impairment

The rats were tested for their ability to remember which of 18 holes, around the periphery of a circular platform, led to a dark tunnel which allowed them to shelter from the bright illumination (*see* Methods). The toxin group learnt this task more slowly than the controls, taking 12 trials rather than 7 (6 days against 3) to reach a group mean of less than two errors per rat per trial. After the fourteenth trial, the location of the escape tunnel was changed, and relearning was followed for as long as the rats would perform the task (after a further 6 trials several rats stopped entering the goal box when they found it). The toxin animals relearned the task less well than the controls (fig. 2); during the first 2–3 relearning trials we formed the impression that the controls rats persevered with the old site more firmly than the toxin group, but we were unable to demonstrate this objectively. The difference in the number of errors made by the two groups was statistically significant (median total errors on trials 1–4 were 47 for the toxin group vs 30 for the control, $P = 0.002$, two-tailed Mann-Whitney U test; or group means of 46.5 vs 33.0; fig. 2D). The learning curves were essentially the same whether plotted as the number of errors made (fig. 2A), or as the time taken to find the correct hole (fig. 2B). Indeed, errors and latency were highly correlated and, most importantly, had the same relationship for the controls and the toxin group (fig. 2C), which suggests that the toxin rats were moving as quickly as the controls, and hence that their impairment is of learning ability rather than, for instance, of locomotion or of aversion to bright light.

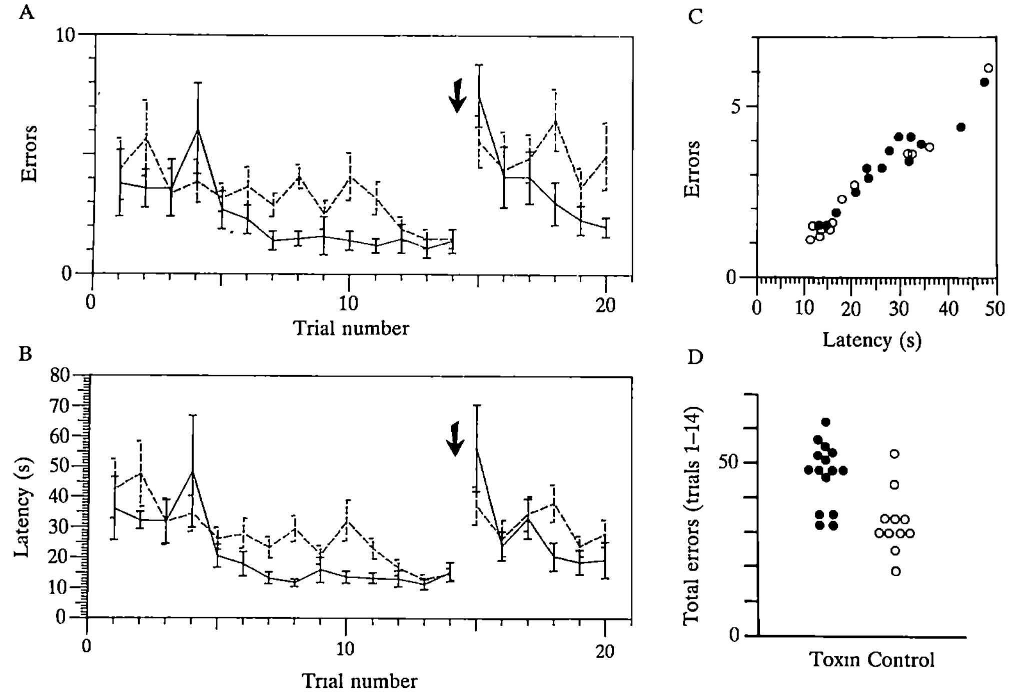

FIG. 2. Circular platform maze: 13 previously epileptic rats (A, B, broken curves; C, filled circles) compared with 10 controls (solid curves; open circles) made more errors (A, means for each trial. D, totals for each animal over trials 1-14), and took longer to find the correct hole (B). The number of errors and the latency were highly correlated for both experimental groups (C, correlation coefficients for previously epileptic group = 0.975, n = 13, and for control group = 0.959, n = 10), and moreover had the same relationship for both groups (analysis of variance of regression coefficients: df = 2, 24, F = 1.24, $P = 0.31$). The position of the goal box was changed by 120 deg after trial 14 (A, B, arrows) to examine the rate of relearning. The symbols for the control and toxin groups are maintained in the remaining figures.

Physiological Measurements

The commissural input to CA3 pyramidal cells was investigated in terminal experiments under 1% halothane anaesthesia, 7-13 weeks after completion of the behavioural experiments (16-22 weeks after injection). As this is a reciprocal pathway between the two hippocampi, its stimulation elicited both orthodromic and antidromic components in CA3 (marked ● and ▲, respectively, in the evoked potentials in fig. 3). Fortunately the axons in this pathway are not randomly arranged (Andersen *et al.*, 1973) and the optimum stimulus site for the antidromic component was typically 300-500 µm dorsal to that for the orthodromic (fig. 3). This greatly simplified measurement of the synaptic potential, which occurs between the two population spikes, and tends to be obscured by them. The precise separation of the respective optimum stimulus sites appeared to be less in the toxin group (312 ± 31 µm, for the focal recording site, 332 ± 44 µm for the medial; n = 13) than in the control group (512 ± 63 µm focal, 416 ± 73 µm medial; n = 10; means ± SEM). These differences between the toxin and control-injected rats were statistically significant for the focal site ($P = 0.004$, Students' unpaired t test, two-tailed), but not for the medial site ($P = 0.30$). It remains to be established whether or not they have any biological significance, for instance whether they reflect some rearrangement in the commissural axons, or a change in recurrent inhibition. The antidromic component was useful both because it confirmed that the recording electrode was indeed in CA3 (and not in the neighbouring CA1 region which does not project through the commissures), and because it provided an indication of the number of CA3 pyramidal neurons present. In fact a 16 V stimulus elicited an antidromic spike at the focal site of 9.0 ± 0.6 mV in the toxin-injected rats, and 9.8 ± 0.7 mV in the controls. At the medial site the same stimulus elicited spikes of 7.4 ± 0.5 mV and 5.8 ± 0.9 mV, respectively, in the two groups. There were no significant differences in antidromic spike height between the two groups (focal site, $P = 0.42$; medial site, $P = 0.14$; Student's t test, two-tailed), which strongly suggests that there was no substantial loss of CA3 pyramidal cells in the toxin group.

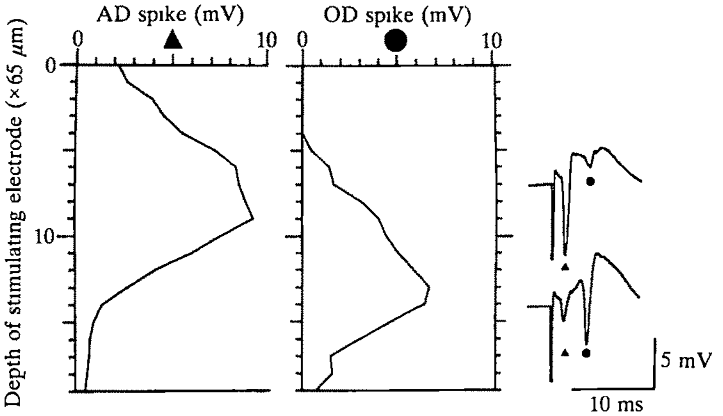

FIG. 3. Lowering the stimulating electrode through the fimbria (commissural pathway) altered the form of the evoked potential recorded in contralateral CA3 cell body layer, the antidromic population spike (AD, ▲) predominating with more superficial sites and the orthodromic or postsynaptic (OD, ●) with deeper sites. Step size was 65 μm. (Calibrations for the evoked potentials = 5 mV, 10 ms).

Postsynaptic Responses from CA3

Once the stimulus site for the orthodromic component of the commissural-CA3 response was optimized, we systematically varied the stimulus strength in order to determine the responsiveness of the pyramidal cells. The relationship between stimulus strength and postsynaptic population spike at the 'focal' recording site is plotted in fig. 4B for each of the rats. The toxin-injected group (dashed lines, $n = 13$) cluster below and to the right of the controls (solid lines, $n = 10$), and thus tended to have smaller population spikes for a given stimulus strength. This can be seen more clearly when these data are averaged (fig. 4D), the toxin animals having population spike amplitudes 0.1–0.5 of those for the controls for stimuli in the range 3–20 V. What this difference represents in terms of evoked potentials is demonstrated in

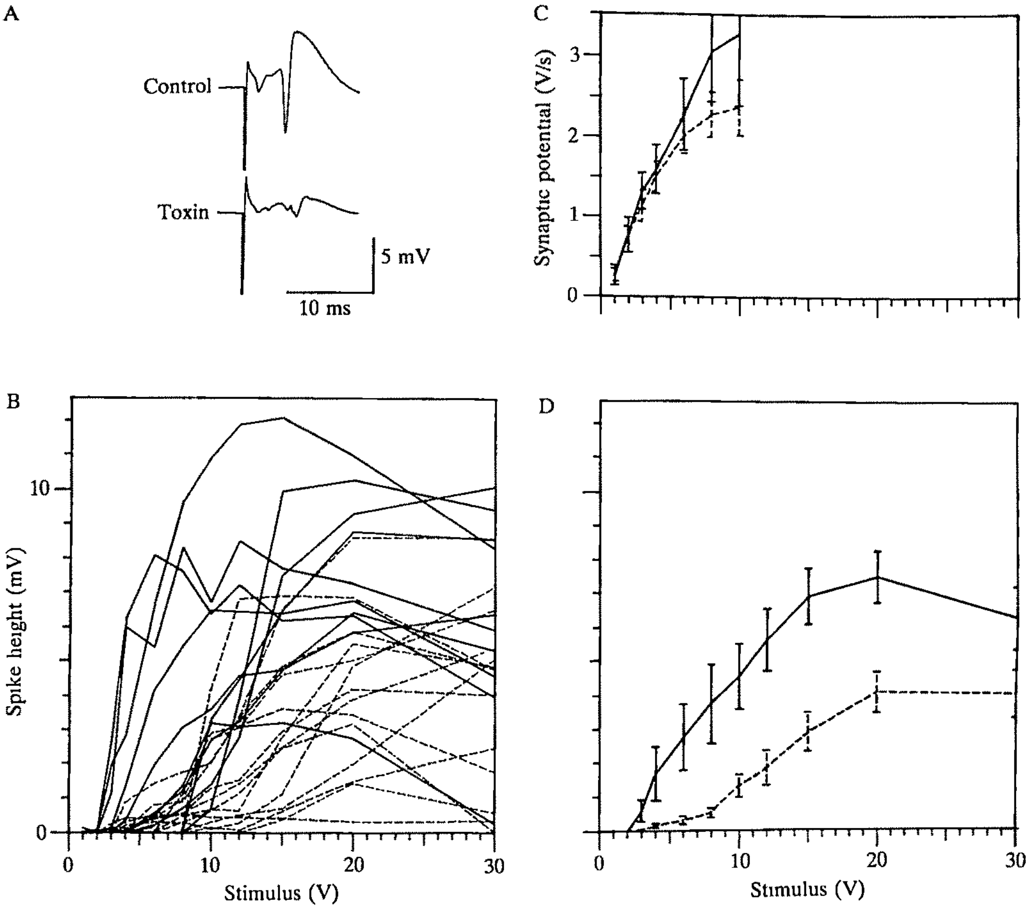

FIG. 4. 'Focal' site stimulus-response curves. Recordings were made from CA3 close to the injection site. Individual (B) and group mean (D) population spikes are plotted against the strength of the stimulus to the commissural pathway (13 in toxin-injected group, 10 in control) The mean rate of rise of the synaptic potential or population EPSP is also plotted (C). The evoked potentials (A) have been selected as the closest match to the respective group mean population spikes for 12 V stimuli. (Error bars (C, D) are ± 1 SE and indicate the dispersion of the data; *see text* for the statistical analysis.)

fig. 4A where individual traces have been chosen as the closest match to the mean population spike size for their respective groups. The difference in population spike size between the two groups cannot be attributed simply to a smaller synaptic input as the component of the evoked potential generated by the excitatory current ('synaptic potential', fig. 4C) was the same in the two groups, over the range of stimuli for which it could be measured reliably (0–6 V).

The statistical analysis of stimulus-response data for the postsynaptic population spike was complicated by the involvement of several processes. There was a considerable variation in spike threshold, which was significantly higher in the toxin-injected rats ($P = 0.032$, t test, two-tailed). The spikes then increased with stimulus strength up to about 20–30 v, beyond which the relationship reversed, presumably as a result of inhibition evoked by the large volleys. In order to avoid the complications thus introduced at both ends of the range of stimuli, we restricted the data to the range of 10–15 V; analysis of variance of these restricted data demonstrated a significant effect of the toxin injection (df = 1, 20, F = 8.12, $P = 0.0099$).

Correlation of Behavioural and Physiological Results

The tetanus toxin-injected group of rats exhibited significant decreases both in the ability to learn the circular platform task, and in the amplitude of the commissural-CA3 population spike. An important question relevant to the causal relationship between these measures is whether or not they are correlated. Taking the data as a whole, there were significant correlations between the behavioural score (total errors over trials 5–14) and measures of the physiological response at the 'focal' site: for the population spike threshold, the Spearman rank correlation coefficient $r_s = 0.62$, $P = 0.002$, $n = 23$; and for spike amplitude, at 10 V, $r_s = 0.70$, $P < 0.001$, $n = 23$; and at 12 V, $r_s = -0.58$, $P = 0.003$, $n = 23$. However, we did not find correlations between these measures within either of the experimental groups.

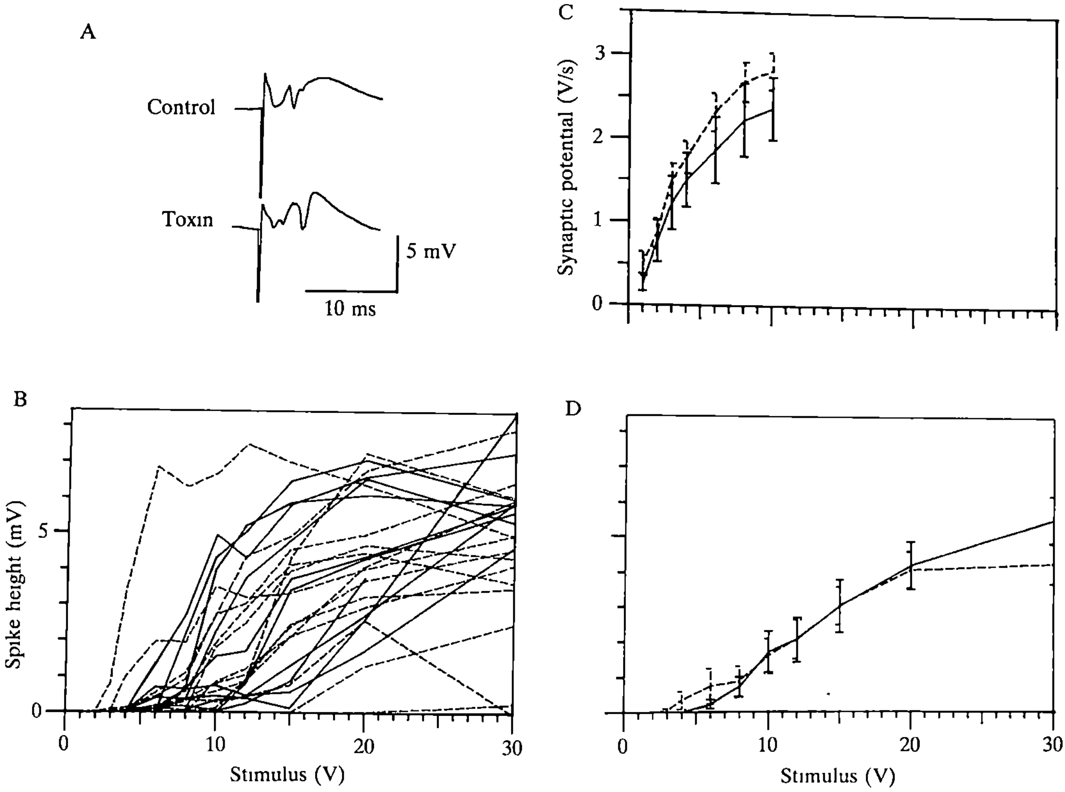

FIG. 5. Medial site stimulus-response curves from a recording site approximately 2.3 mm from that used in fig 4

Responses from Medial Recording Site

The recording site used for the results described above was 3.5 mm lateral to the midline, close to the location of the earlier injection site. Simultaneous recordings were made from a second site in CA3, 1.5 mm lateral to the midline (at a total distance of 2.25 mm from the first site). These two sites resembled each other in exhibiting no difference in the synaptic potentials recorded in the two groups of experimental rats (fig. 5C). However, the stimulus-response curves obtained for the medial site (fig. 5B, D) also showed no differences between the two groups in their population spike thresholds ($P = 0.90$, t test) or their population spike amplitudes (df = 1, 21, F = 0.00, $P = 0.999$), in marked contrast to the more lateral ('focal') site.

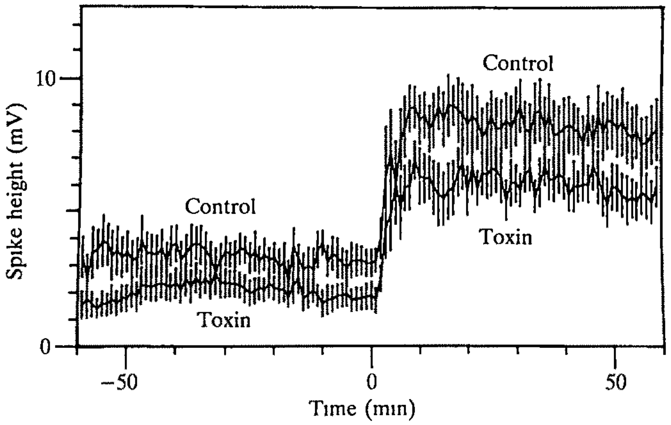

FIG. 6. Time course of long-term potentiation; mean (±SEM) population spikes for 6 control and 6 toxin-injected rats have been plotted for 1 h before and 1 h after the conditioning train of 50 stimuli at 250/s Stimulus strength was constant in each rat.

Long-term Potentiation (LTP)

The prolonged duration of LTP has suggested that this phenomenon might have a role in learning and memory and, more specifically, that disruption of LTP could be associated with the impaired learning found following injection of tetanus toxin into the hippocampus. We recorded CA3 responses to commissural stimulation for 1 h before and up to 4 h after a conditioning train of 50 stimuli at 250/s. The stimulus strength was chosen to give a small but distinct postsynaptic population spike. Larger stimuli could cause difficulties, for instance by eliciting epileptic activity following the conditioning train (this happened to 3 animals from each group). Six toxin and 6 control rats gave trouble-free LTP runs for 1 h before and after the conditioning train; the postsynaptic population spikes have been averaged and are plotted in fig. 6. It is clear that both groups exhibited LTP which persisted for at least 1 h, with the spike increasing approximately three-fold in both groups (× 3.2 for the toxin group, and × 2.7 for the controls, comparing the period from 10 to 30 min after conditioning with the 20 min immediately preceding conditioning). No differences in the time course of LTP were noted in those cases followed for longer periods. The only obvious difference between the two groups was the size of the test response chosen at the start of the LTP experiment, which presumably was an unintentional consequence of the observations described above (fig. 4).

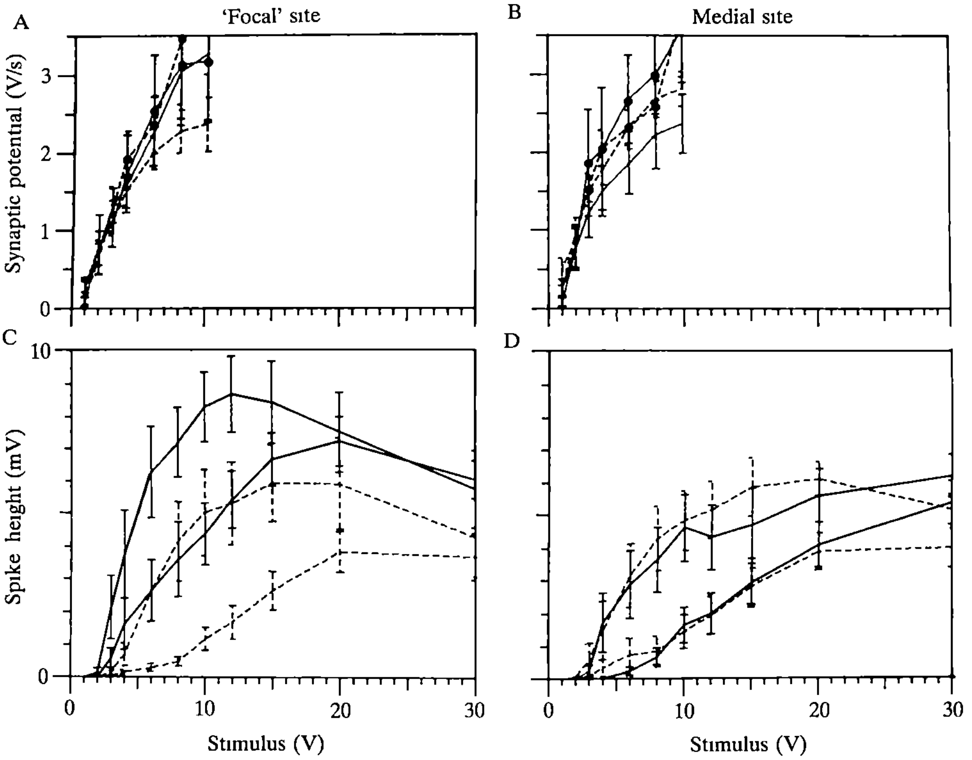

FIG. 7. Long-term potentiation; stimulus response curves were obtained from recording sites at 3.5 mm lateral ('focal', A, C) and 2.0 mm lateral ('medial', B, D), in the toxin-injected group (broken curves; n = 13, 8, pre- and post-LTP, respectively), and in the control group (solid curves; n = 10, 8). The recordings were made 1 h before and 1 h after the conditioning train: in each case the population spikes (C, D) were clearly potentiated (therefore the post-LTP curves are uppermost), while the synaptic potentials were not (A, B; post-LTP data points have been marked ● where they can be distinguished).

Stimulus-response curves were taken 1 h before and 1 h after the conditioning train. The relation between the population spike and stimulus strength became much steeper after the conditioning train in both groups of rats, at both recording sites (fig. 7C, D, respectively; control, solid curves; toxin, dashed curves; upper curves are post-LTP in each case). The extent of LTP appeared broadly similar in the two groups of rats, although it was difficult to select a useful measure of potentiation for the 'focal' site given the difference between the pre-LTP curves for the two groups (fig. 7C); at the more medial site the data for the two groups were almost identical (fig. 7D). The divergence of the pre- and post-LTP curves reached a maximum at about 10 V in each case, which is close to the stimulus strengths used for the conditioning trains. Changes in the spike threshold were small or nonexistent. The clear and significant potentiation of the population spikes found in these LTP experiments was not accompanied by any significant change in the synaptic potentials recorded at either site, in either group of animals (fig. 7A, B; filled circles indicate the post-LTP data where they can be distinguished), so that the potentiation was of the E-S type according to Andersen *et al.* (1980).

DISCUSSION

Injection of tetanus toxin into the dorsal hippocampi of rats caused recurrent epileptic seizures similar to those described previously for more ventral injection sites. Once the rats had recovered from their seizures, they learnt a circular platform task less well than control-injected rats. This learning impairment was associated with a reduction in the physiological responses of CA3 pyramidal cells to commissural stimuli; long-term potentiation of this pathway appeared normal, at least over periods of a few hours. The depression of CA3 pyramidal cells provides the most reasonable physiological explanation for the behavioural impairment (*see also* Brace *et al.*, 1985).

Learning Impairment

The precise role of the hippocampus in behaviour in general, and in learning and memory in particular, remains the subject of debate (*see* open peer commentary following Rawlins, 1985; O'Keefe and Nadel, 1978). Following remission from the tetanus toxin seizures, performance was impaired both on the circular platform task used in this study, and on the radial arm maze task used in the complementary study of Brace *et al.* (1985). The most significant feature that these two tasks share is their strong dependence on the interpretation of distal, spatial cues. However, they differ in the use that is made of this information. The circular platform task requires the rat to learn the location of a goal box which remains fixed in relation to distal cues, so that the task can be considered predominantly one of reference memory. In contrast, the radial arm maze requires that the rat remembers which arms it has already visited during each trial, if it is not to visit any arm twice and thus reduce its food reward; this task can be considered predominantly one of an intermediate-term memory or a 'working memory'. The radial arm maze also has a significant procedural component, in that rats needed several days pretraining in order to learn how to search for food on the maze, while rats needed no pretraining to explore the holes in the circular platform, nor to enter the goal box when they found it.

Barnes (1979) has previously reported differences in performance of the circular platform task between old and young rats, broadly similar to those found here between postepileptic and control rats. Thus the performance of young and control rats levelled off at fewer errors than the old and toxin rats, respectively. There were minor differences between these two studies. The scores of our control and toxin rats did eventually converge, after a further 6 trials. Barnes (1979) changed the goal position sooner than we did, therefore it is impossible to say whether the scores of her two groups would have converged with further trials. Our rats made fewer errors on the first phase of the experiment than in that of Barnes (1979), but relearned the task less well after the goal position was changed.

Physiological Changes

Previous reports had speculated that abnormalities in LTP might be associated with the persistent impairment of learning and memory following intrahippocampal tetanus toxin (George and Mellanby, 1982; Mellanby *et al.*, 1982). However, LTP of the commissural input to CA3 pyramidal cells appeared to be normal over the time span of a few hours, suggesting that a simple disruption of LTP cannot explain the learning deficit.

Usually LTP occurs both in the synaptic wave (or population EPSP), and the population spike, and probably reflects an increase in synaptic drive. In contrast, LTP in both groups of rats in this study occurred only in the population spike and not in the synaptic wave, suggesting that the potentiation reflected an increase in postsynaptic excitability. This has been termed E-S potentiation (Andersen *et al.*, 1980). These two types of LTP appear to be quite distinct (Abraham *et al.*, 1985). The precise mechanisms involved, and the reasons why E-S potentiation should be favoured in the CA3 region under the conditions of the present experiments remain to be resolved; however, LTP was not altered by the tetanus toxin treatment. More persistent components of LTP (with a time course of 3–7 days) can be induced by repeated conditioning trains in chronic experiments, and may be more relevant to learning (Barnes, 1979). On the other hand, the depressed excitability of the CA3 pyramidal cells described in the present paper and in Brace *et al.* (1985) provides a more straightforward basis for the learning deficit following tetanus toxin.

The depression of CA3 responses was marked (to 0.1–0.5 of control values) close to the site of the injection of some months earlier, but was not found at a site 2.25 mm towards the septal pole of the hippocampus (i.e. more medially). At first sight this suggests that the long-term depression may be a consequence of the earlier direct exposure to the tetanus toxin. However, a depression was also observed in the parallel study of Brace *et al.* (1985), where the injection was made into a site in the ventral hippocampus, some 4.2 mm from the dorsal recording site used in both these studies. The topology of the neuronal depression remains to be investigated in detail; possible explanations combining these respective studies might involve, for instance, either some protective influence of surround inhibition (Dichter and Spencer, 1969), or the precise topology of local axon projections involved in the spread of either seizures or toxin.

The present observations do not identify the cellular mechanism of the long-term postepileptic depression of CA3 pyramidal cells. No loss of pyramidal cells was discernible either from previous qualitative anatomical reports, or from the present measurements of the optimal antidromic spike (fig. 3). Similarly there was no evidence of a loss of excitatory afferents (fig. 4; unpublished histological observations using Timm's stain). The only evidence for some anatomical rearrangement in the toxin-injected rats was the smaller distance separating the optimal antidromic and orthodromic stimulus sites in the commissural pathway; our recent observations, however, suggest this could have resulted from weakened recurrent inhibition (Williams and Jefferys, 1985).

Persistent changes in neuronal function have not been found widely following epilepsy, perhaps because they are obscured by neuronal damage or loss (e.g., kainic acid seizures: Ben-Ari *et al.*, 1980; Kessler and Markowitsch, 1983). The 'kindling' model is interesting in the present context, as it has not yet been associated with any gross histopathology, and by definition it causes permanent changes in neuronal properties (a reduction in seizure threshold; Goddard *et al.*, 1969). Recent work suggests that kindling may result from a progressive weakening of inhibition (Kamphuis *et al.*, 1985; Wadman and Lopes da Silva, 1985). In contrast, most previous studies had demonstrated the opposite, namely a persistent enhancement of the GABA/inhibitory system days–weeks after kindling (Leibowitz *et al.*, 1978; Tuff *et al.*, 1983*a*; Tuff *et al.*, 1983*b*; King *et al.*, 1984; Maru and Goddard, 1984; Sato and Moriwake, 1984; *see* Burnham *et al.*, 1983). This latter paradoxical result could represent an adaptive response in tissue surrounding the kindled focus, perhaps analogous to the (?adaptive) neuronal depression reported here for the tetanus toxin model. However, different mechanisms appear to be involved in the two models: the depression with tetanus toxin was not due to a simple enhancement of inhibition because feed-forward and recurrent inhibition were persistently weakened, if they changed at all (preliminary report: Williams and Jefferys, 1985).

This paper, together with the complementary report by Brace *et al.* (1985), demonstrates that, following remission from tetanus toxin seizures, rats exhibited both behavioural and electrophysiological dysfunction. The behavioural impairments in these two studies were on tasks which have in common a substantial spatial component. The physiological impairment was a persistent depression of hippocampal CA3 pyramidal neurons. These results support the idea that the hippocampus has an important role in the interpretation of spatial information.

We clearly wish to know whether a similar long-term neuronal depression occurs in human partial seizures. Ultimately this question will have to be resolved by measurements of neuronal activity in patients (or in biopsied tissue). However, indirect evidence may come from the observation that interictal epileptic foci in man often exhibit hypometabolism (Engel *et al.*, 1982). A question which requires an early answer is whether the tetanus toxin model causes a local hypometabolism in addition to the long-term neuronal depression. Therefore, although our interest has been in the learning impairment in this animal model, we believe that the long-term neuronal depression found here will prove relevant to a wider range of behavioural and other functional abnormalities in complex partial seizures and other epilepsies.

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PERIPHERAL SENSORIMOTOR AND AUTONOMIC NEUROPATHY ASSOCIATED WITH SYSTEMIC LUPUS ERYTHEMATOSUS

CLINICAL, PATHOLOGICAL AND IMMUNOLOGICAL FEATURES

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SUMMARY

The clinical features and pathological findings in the sural nerves are described of 7 patients with peripheral neuropathy; in 4 cases the criteria for diagnosis of systemic lupus erythematosus (SLE) were satisfied and in 3 other cases there was serological evidence of an undifferentiated connective tissue disease, most probably SLE. The peripheral neuropathy was of a chronic sensorimotor type with predominantly sensory features and gradual onset. In 2 cases the presentation was asymmetric. One patient had autonomic dysfunction. The pathological findings in the biopsied sural nerves were those of axonal degeneration and vasculitis. In 6 nerves there was increased expression of Class II (Ia) antigen within the nerve fascicle, perineurium and within endothelial cells.

INTRODUCTION

It is recognized that the central nervous system is frequently affected in systemic lupus erythematosus (SLE) (Harvey *et al.*, 1954; Dubois and Tuffanelli, 1964; Johnson and Richardson, 1968; Richardson, 1980) and damage is mainly the result of destructive changes in the walls of small blood vessels (Johnson and Richardson, 1968; Ellis and Verity, 1979; Richardson, 1980). Peripheral neuropathy in SLE has been less well studied. In large clinical series the frequency of involvement of the peripheral nervous system has ranged from 2 to 18% (Clark and Bailey, 1956; Bennett *et al.*, 1961; Dubois and Tuffanelli, 1964; Johnson and Richardson, 1968; Estes and Christian, 1971; Cheatum *et al.*, 1973; Feinglass *et al.*, 1976; Gibson and Meyers, 1976; Lee *et al.*, 1977; Abel *et al.*, 1980). The peripheral neuropathy may be of the progressive symmetric sensorimotor type, mononeuropathy, multiple mononeuropathy, or a radiculoneuropathy (Bailey *et al.*, 1956; Richardson, 1980; Conn and Dyck, 1984). There have been several reports of the pathological changes in the peripheral nerve; vascular changes have been noted by some authors (Heptinstall

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and Sowry, 1952; Bailey *et al.*, 1956; Goldberg and Chitanondh, 1959; Hughes *et al.*, 1982) but not by others (Scheinberg, 1956; Lewis, 1965; Johnson and Richardson, 1968). Although destructive changes in the small blood vessels are likely to contribute to the pathogenesis of the peripheral neuropathy associated with SLE, other factors such as deposition of immune complexes or damage by antibodies to components of neural tissue may be important (Richardson, 1980; Conn and Dyck, 1984). Because of the uncertainty about the pathology and pathogenesis of the condition we report the clinical and pathological features of the peripheral neuropathy in 7 patients with peripheral neuropathy associated with SLE.

METHODS

Patient Selection and Diagnostic Criteria

All patients had been referred for sural nerve biopsy after a clinical diagnosis of probable SLE and peripheral neuropathy had been made, using the ARA criteria (Tan *et al.*, 1982). Control sural nerve was obtained from 3 subjects in whom the nerve was normal and from 5 patients with toxic neuropathy (nitrous oxide, organophosphate, hexacarbon, hydralazine).

Nerve Conduction Studies

The techniques are standard in our laboratory and have been described in detail elsewhere (Walsh and McLeod, 1970). Motor conduction velocities were determined in the median, ulnar, and peroneal nerves, using surface electrodes. Sensory action potentials were recorded with surface electrodes from the median and ulnar nerves at the wrist on stimulating the index and little fingers, respectively, through ring electrodes.

Histological Techniques

The techniques have been fully described elsewhere (Walsh and McLeod, 1970; Low *et al.*, 1978). Whole sural nerve biopsy was performed at the level of the lateral malleolus under local anaesthesia. The nerve was divided into 3–5 portions, each about 1 cm in length. One piece of each nerve was fixed in picric acid, embedded in paraffin and cut transversely and longitudinally in sections of 5 μm thickness. The sections were stained with haematoxylin and eosin, and with Congo red. Another piece of nerve was fixed in Flemming's solution for 24 h, dehydrated in alcohol, embedded in paraffin wax, and cut transversely in serial sections of 5 μm thickness. The sections were stained with Kultschitzsky's haematoxylin and counterstained with Van Gieson. A third piece was stained for 24 h in 1% osmium tetroxide, macerated in glycerol and teased apart under a dissecting microscope in order to isolate single nerve fibres. A fourth piece was fixed in cold 2.5% glutaraldehyde in 0.1 M cacodylate buffer for 3 h followed by Dalton's chrome-osmium for 90 min. The tissue was dehydrated in graded concentrations of ethanol, passed through acetone and embedded in Spurr's medium. Sections were cut with glass or diamond knives and stained with uranyl acetate and lead citrate and examined in a Philips 200 or 201 electron microscope. Additional portions of nerves were also obtained. One portion was fixed immediately in Dalton's chrome-osmium and then processed as described for glutaraldehyde-fixed tissue. Another was frozen in liquid nitrogen and from this portion cryostat sections were cut for immunohistochemical staining.

Morphometric Studies

Photomicrographs of plastic-embedded, toluidine blue stained sections of fascicles selected according to the methods described by Dyck *et al.* (1979) were printed on photographic paper at an enlargement of × 1100. The number of fibres not undergoing active degeneration was counted and their external diameters measured with a Zeiss TG23 particle size analyser set in the linear mode. The diameter of the light spot was adjusted to approximate to the mean diameter of each fibre. The endoneurial area of the fascicles was measured with a digitizer attachment (HP9864A) of a Hewlett-Packard 9815A programmable calculator. The fibre density was calculated as the number of fibres/mm^2 of intraperineurial area. Histograms of fibre diameter distribution were drawn with a plotter (HP9862A). Axons of unmyelinated fibres were counted and their diameters measured as described above, with a Zeiss TGZ3 particle size analyser set in the linear mode on prints at a final magnification of × 8544. The numbers of denervated Schwann cell subunits and collagen pockets were counted on the prints used in the measurement of unmyelinated fibres.

Immunofluorescence

Direct immunofluorescence was performed on thin sections of frozen nerve biopsy specimens, and frozen normal human peripheral nerve, using FITC conjugated sheep antihuman immunoglobulin antibodies (Wellcome). The sections were examined immediately under a Zeiss microscope. Each nerve was examined on at least three occasions.

Indirect Immunoperoxidase

Acetone fixed air-dried cryostat sections of sural nerve were incubated in mouse antihuman monoclonal antibodies to several lymphocyte and monocyte antigens, diluted 1 in 80 for 30 min. Antibodies to T4 (helper), T8 (suppressor), T11 (total) T cell subsets and Ia antigen were obtained from Coulter Immunology (USA) and antibodies to T10 (activated lymphocytes) and macrophages (M1) from Ortho Diagnostic Systems (New Jersey, USA). Sections were washed then incubated in HRP conjugated rabbit antimouse immunoglobulin (Dakopatts, Glostrup, Denmark) diluted 1 in 25 for 30 min. After further washing the reaction product was visualized with 0.04% diaminobenzidine. Control nerve biopsy tissue was processed in an identical manner.

RESULTS

Clinical Features

The clinical and diagnostic laboratory features are summarized in Table 1. All patients were females. Other causes of peripheral neuropathy were excluded by history, physical examination and appropriate laboratory tests. All patients were referred for sural nerve biopsy after a presumptive clinical diagnosis of SLE and peripheral neuropathy had been made. Four patients (Cases 1-4) were classified as definite cases of SLE because they satisfied four of the ARA criteria for the diagnosis (Tan *et al.*, 1982). Three other patients (Cases 5-7) were included in the study since they had markedly elevated titres of antinuclear factor, a finding strongly suggestive of the diagnosis of SLE. In 1 of these cases, three of the ARA criteria were satisfied and in 2, two criteria were satisfied.

Peripheral neuropathy developing in established SLE (*Cases 1-3*). The age of onset of symptoms of peripheral neuropathy ranged from 18 to 64 yrs, and the symptoms of peripheral neuropathy first became evident at intervals of 2 to 29 yrs after the first systemic manifestations of SLE. In 2 patients (Cases 1, 2) there was an asymmetric presentation of the neuropathy; in Case 1 the patient was investigated for pain and numbness in one foot, attributed to a peroneal palsy, three years before developing numbness in a distribution over all four limbs and Case 2 presented with

TABLE 1. CLINICAL AND DIAGNOSTIC LABORATORY FEATURES OF SLE NEUROPATHY

		Age at onset (yrs)		*ARA criteria for SLE*											
Case	*Sex*	*Neuropathy*	*Systemic manifestations*	*Malar rash*	*Discoid rash*	*Photosensitivity*	*Oral ulcers*	*Arthritis*	*Serositis*	*Renal disorder*	*Neurological disorder*	*Lymphopenia*	*Immunological disorder*	*ANA*	*Peripheral neuropathy*
1	F	63	58	+		+		+					C4 reduced	1 500	Onset pain, numbness one foot Gradual progression Predominantly sensory neuropathy
2	F	64	62					+				+	Direct Coombs +ve DNA binding increased Lupus band test +ve C3, C4 reduced	1 640 (homogeneous)	Subacute onset pain, numbness one foot Asymmetric sensorimotor neuropathy
3	F	44	15	+	+	+								1 160 (speckled)	Gradual onset Painful, predominantly sensory symmetric neuropathy
4	F	18	10			+		+				+	DNA binding increased Rheumatoid factor +ve Lupus inhibitor present Circulatory immune complex C4 reduced	1 640 (homogeneous)	Symmetric sensory neuropathy Autonomic neuropathy
5	F	67											Anti-ds DNA binding increased VDRL false +ve C4 reduced	1 2560 (speckled)	Gradual onset numbness one foot Asymmetric sensorimotor neuropathy
6	F	63										+	Anti-ds DNA −ve RF +ve Lupus band test +ve	1 2560 (homogeneous and speckled)	Gradual onset of symmetric sensory neuropathy
7	F	43	43	+								+	Anti-ds DNA −ve RF +ve. VDRL −ve Lupus band test +ve	1 2560 (speckled)	Gradual onset slowly progressive symmetric predominantly sensory neuropathy

numbness of one foot and leg three weeks before developing a generalized symmetric sensorimotor neuropathy. All 4 patients finally had the clinical features of a generalized sensorimotor neuropathy in which the sensory features were predominant. Pain was a prominent feature in 3 patients. Two patients (Cases 1, 3) were treated with corticosteroids, but without any clinical evidence of improvement in the neuropathy.

Peripheral sensory and autonomic neuropathy in established SLE (*Case 4*). Case 4, a Vietnamese girl aged 18 yrs, had an 8-yr history of skin photosensitivity, weight loss, arthralgia, hair loss, diarrhoea, absence of tears and impairment of sweating. There was clinical and electrophysiological evidence of a symmetric sensory neuropathy. She was treated with corticosteroids without effect. Autonomic function studies were performed and the results were as follows.

Sweat test: there was an abnormal response with patchy sweating on the trunk but no sweating on the limbs. Change of blood pressure with posture: the values obtained were 92/63 mmHg supine and 81/59 mmHg erect. Heart rate variation with respiration: the ratio of the longest R-R interval in expiration to the mean shortest R-R interval in inspiration (E : I ratio) was 1.04 (normal $\geqq$ 1.10). Heart rate response to standing: the ratio of the R-R interval at 30th beat to the R-R interval at the 15th beat (30 : 15 ratio) was 0.95 (normal $\geqq$ 1.03). Valsalva ratio: the ratio of the longest R-R interval to the shortest R-R interval during a Valsalva manoeuvre (Levin, 1966): this was 1.25 (normal $\geqq$ 1.45). Valsalva response: when the blood pressure was recorded with an intra-arterial catheter the Valsalva response was blocked with no overshoot of systolic blood pressure and no bradycardia in phase IV. Pupillary responses: both pupils contracted with the installation of 2.0% methylcholine, consistent with parasympathetic denervation. Plasma noradrenaline: there was no increase in levels after changing from the supine to the standing position.

These findings are consistent with impairment of sympathetic function (abnormal sweat test; no increase in noradrenaline levels with change in posture) and impaired parasympathetic function (abnormal heart rate response to breathing and standing and abnormal Valsalva response). The absence of orthostatic hypotension in the presence of a blocked response to Valsalva manoeuvre is consistent with incomplete damage to the autonomic nervous system (Johnson *et al.*, 1969).

Patients presenting with peripheral neuropathy (*Cases 5–7*). Three patients aged 43–67 yrs presented with peripheral neuropathy and on investigation had high titres of antinuclear antibody. Although only three of the ARA criteria for SLE were satisfied in Case 7 and two in Cases 5 and 6, there was no clinical evidence of any other autoimmune or connective tissue disease. All patients had symmetric predominantly sensory neuropathies; in Case 5 the onset was asymmetric with numbness in one foot for two years before the symptoms became more generalized. Two patients (Cases 6, 7) were treated with corticosteroids and improved.

Laboratory Investigations

Haemoglobin, platelets, and serum electrolyte concentrations were normal. In 4 patients there was a lymphopenia (less than 1,500 lymphocytes/mm^3). The erythrocyte sedimentation rate (ESR) was elevated (32–105 mm/h) in 5 patients (Cases 1, 3–5, 7). In 2 patients there was an increase in serum IgG (Cases 2, 4) and in 1 (Case 6) there was an increase in IgM but no paraproteins were detected on immunoelectrophoresis. The cerebrospinal fluid (CSF) was examined in 4 patients; in 2 it was normal (Cases 1, 2) but in the other 2 the CSF protein content was markedly elevated (Case 4, 3.1 g/l; Case 7, 4.55 g/l). The results of serological and immunological studies are summarized in Table 1.

TABLE 2. PATHOLOGICAL FEATURES OF SURAL NERVES

Case	*Blood vessels*	*Density myelinated fibres (fibres × 10³/mm²)*	*Teased fibres* *Myelin ovoids (%)*	*Teased fibres* *Segmental demyelination (%)*	*Electron microscope features*	*Density unmyelinated fibres (fibres × 10³/mm²)*	*Monoclonal antibody staining*
1	Healed vasculitis with perivascular infiltrate	0.85			Chronic axonal degeneration	9.7	Not done
2	Vasculitis with perivascular infiltrate	3.45	40	0	Acute axonal degeneration Infiltrating mononuclear cells	11.6	Monocytes and Ia positive cells within fascicles and around blood vessels T cells in fascicles and increased endothelial Ia around blood vessels
3	Vasculitis	4.76	10	40	Chronic axonal degeneration	22.5	Minimal cellular infiltrate Increased endothelial Ia
4	Intimal hyperplasia and occasional perivascular cells	4.11	30	0	Chronic axonal degeneration	21.3	Few Ia +ve cells mainly perivascular Monocytes and Ia +ve cells mainly perivascular Increased endothelial Ia
5	Intimal hyperplasia but no cells	5.36	5	0	Chronic axonal degeneration	15.2	Increased Ia staining within perineurium, endothelium and within nerve fascicle
6	Mild vasculitis with perivascular infiltrate	3.95	40	5	Chronic axonal degeneration with infiltrating mononuclear cells	9.9	Occasional Ia +ve cells in fascicles Increased Ia in blood vessels and perineurium T cells around blood vessels, some in endoneurium Occasional monocytes in fascicle
7	Mild vasculitis with perivascular infiltrate	6.0	20	20	Chronic axonal degeneration with infiltrating mononuclear cells	27.4	Increased Ia +ve cells in fascicles Increased Ia staining in endothelium Few monocytes and T cells in fascicles and perivascularly

Nerve conduction studies were abnormal in all patients. Motor conduction velocities were mildly reduced in one or more nerves in 4/7 patients. Motor conduction velocities in the peroneal nerve ranged from 29 to 52 $m \cdot s^{-1}$ (mean 39.0; SD 8.41) which may be compared with the control range of 41–56 $m \cdot s^{-1}$ (mean 48.7; SD 4.4) in our laboratory (McLeod and Evans, 1981). The difference is significant ($P < 0.01$, Students' t test). Sensory conduction was abnormal in all patients; in 5 (Cases 1–4, 7) sural nerve action potentials were absent, and in 2 of them (Cases 4, 7) median and ulnar sensory action potentials were also absent. In the remaining 2 patients the amplitude of one or more sensory action potentials was reduced.

Histopathology

The main pathological features are summarized in Table 2.

Light microscopy. Vascular abnormalities were demonstrated in haematoxylin and eosin-stained sections in all nerves in perineurial vessels. In Cases 1, 2 and 3 there was a true vasculitis, with marked thickening of the walls of vessels of all sizes, and infiltration with mononuclear cells in and around the vessels (fig. 1A). In Cases 4 and 5, there were minor changes with thickening of vessel walls, especially of the intima, but little evidence of cellular infiltration. In Cases 6 and 7 there were intimal changes and perivascular cellular infiltration (fig. 1B). The vascular abnormalities ranged from intimal thickening to arteritis. The 2 patients who presented with mononeuritis had the more severe vascular changes.

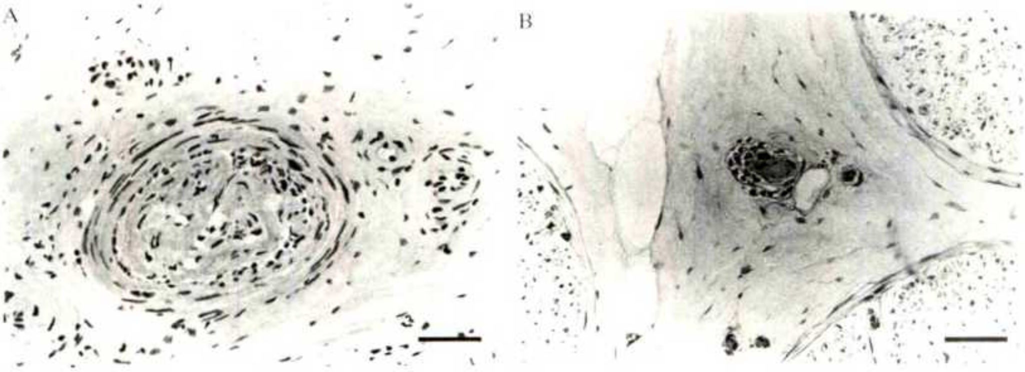

FIG. 1. Vascular abnormalities in blood vessels of sural nerves. A, *Case 1*. Intimal thickening and inflammatory cell infiltration. B, *Case 7*. Inflammatory cell infiltration around small blood vessel. Haematoxylin and eosin. Bars = 50 μm.

In toluidine blue-stained transverse sections there was a reduction in the density of myelinated fibres in the nerves of Cases 1, 2, 4 and 6; in the nerve of Case 2 many fibres were undergoing active axonal degeneration (fig. 2). The density of myelinated fibres ranged from 0.85 to $6.1 \times 10^3/\text{mm}^2$ (mean 4.07, SD $1.7 \times 10^3/\text{mm}^2$) which may be compared with the normal range in our laboratory of $4.8\text{–}8.7 \times 10^3/\text{mm}^2$ (mean 6.64, SD $1.3 \times 10^3/\text{mm}^2$). There was a significant reduction in the mean density in patients with SLE ($P < 0.01$, Students' t test). The fibre diameter distribution of the remaining fibres is shown in fig. 3 where it is apparent that there has been loss of fibres of all diameters.

Teased fibre preparations. In Case 1 so few fibres remained that teasing was not possible. As shown in Table 2, the remaining 6 patients had evidence of axonal degeneration; 3 had evidence of segmental demyelination in some fibres.

Electron microscopy. Electron microscope studies confirmed that axonal degeneration was the predominant pathological change. In all nerves there was loss of myelinated and unmyelinated fibres. Actively degenerating fibres were very

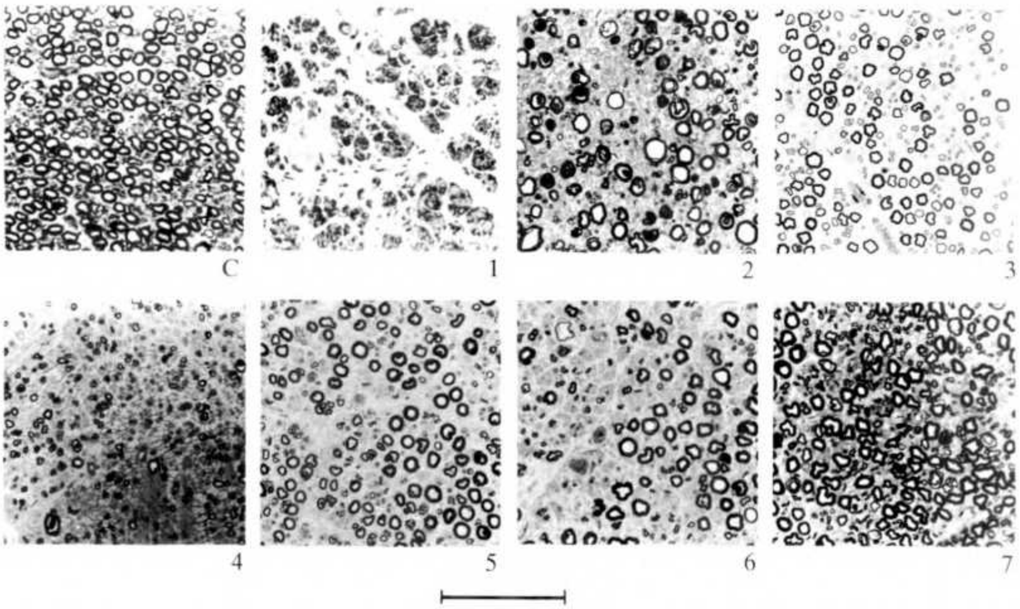

FIG. 2. Transverse sections of fascicles of sural nerves from control (C) and Cases 1–7. Toluidine blue. Bar = 100 μm.

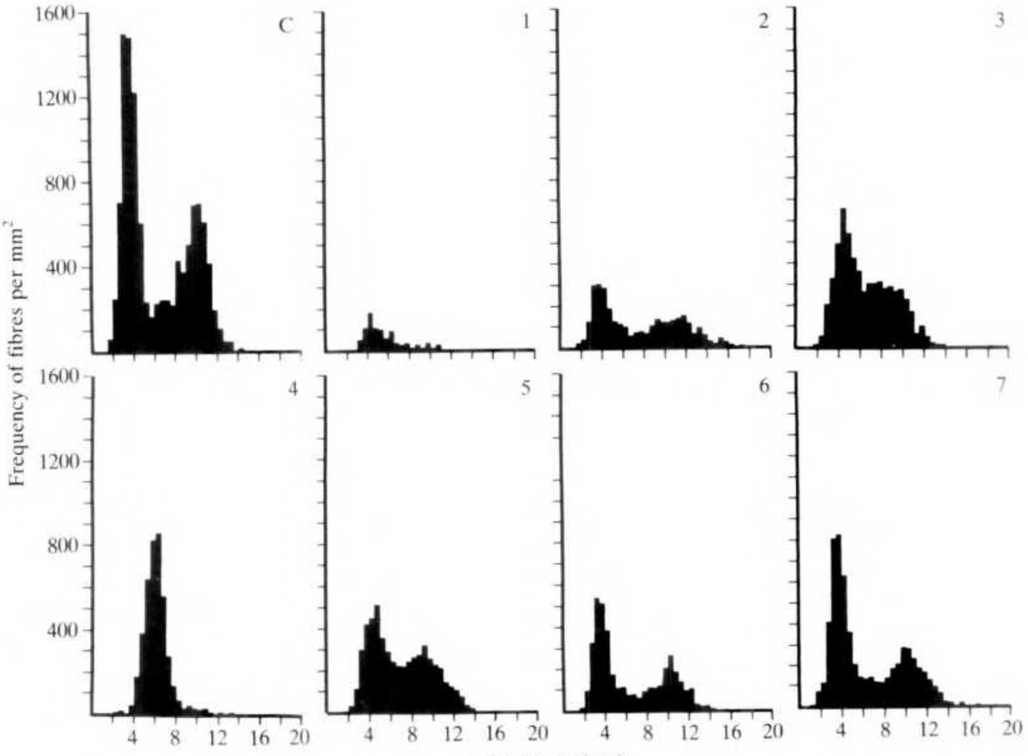

FIG. 3. Myelinated fibre diameter distributions in sural nerve biopsies of control (C) and Cases 1–7.

prominent in one biopsy (Case 2) (fig. 4). In the others there was evidence of chronic axonal degeneration with cluster formation and occasional degenerating fibres. In one nerve (Case 1) there was evidence of severe chronic axonal degeneration with very few myelinated fibres remaining. Mononuclear cells were seen between the nerve fibres in nerves from 3 patients (Cases 2, 6 and 7) (fig. 5).

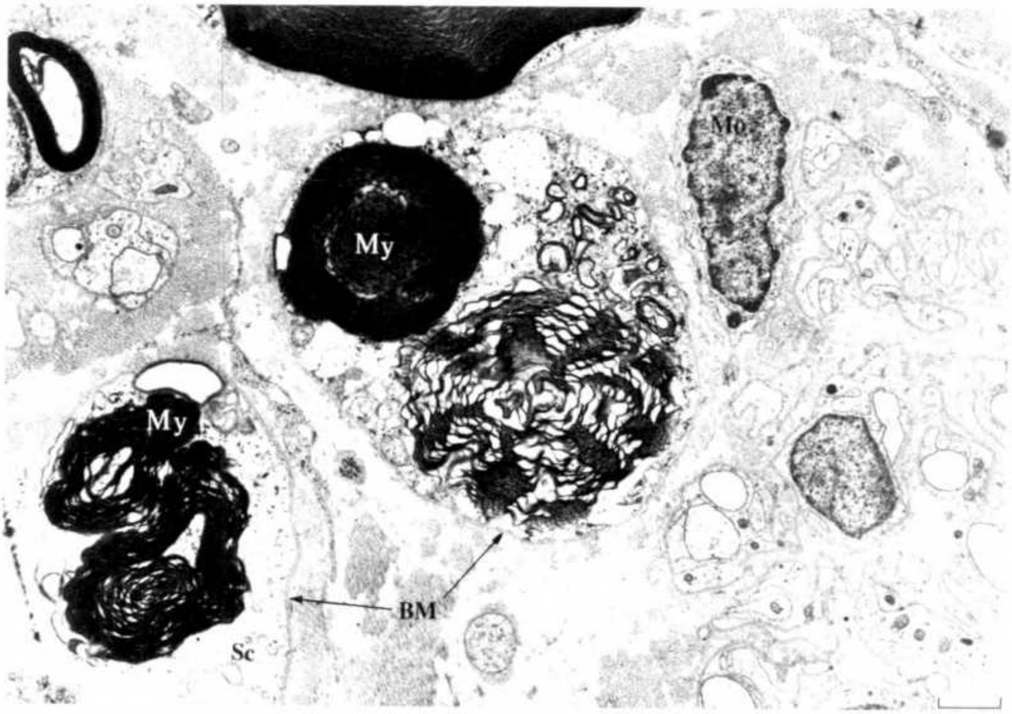

FIG. 4. *Case 2.* Electron micrograph of sural nerve showing active axonal degeneration. Note presence of mononuclear cell (Mo). My = myelin debris; Sc = Schwann cell cytoplasm; BM = basement membrane of Schwann cell. Bar = 1 μm.

Morphometric studies on unmyelinated axons showed a mean density ranging from 9.7 to $27.4 \times 10^3/\text{mm}^2$ (mean 16.8, SD $6.5 \times 10^3/\text{mm}^2$) which may be compared with the control range of $24.7\text{–}51.5 \times 10^3/\text{mm}^2$ (mean 38.0, SD $9.5 \times 10^3/\text{mm}^2$). The difference is significant ($P < 0.002$) and the density fell below the control range in 6 of the 7 patients.

The density of collagen pockets and of empty Schwann cell subunits could not be determined for Case 1. In the remaining patients the density of collagen pockets ranged from 5.4 to $13.0 \times 10^3/\text{mm}^2$ (mean 9.0, SD $2.4 \times 10^3/\text{mm}^2$). The control range of values for our laboratory is $3.5\text{–}9.1 \times 10^3/\text{mm}^2$) (mean 5.7, SD $2.2 \times 10^3/\text{mm}^2$). The difference is significant ($P < 0.05$). The density of empty Schwann cell subunits ranged from 2.7 to $16.7 \times 10^3/\text{mm}^2$ (mean 7.2, SD $4.4 \times 10^3/\text{mm}^2$). The control range is $1.8\text{–}5.5 \times 10^3/\text{mm}^2$ (mean 4.3, SD $1.5 \times 10^3/\text{mm}^2$). The difference is not significant.

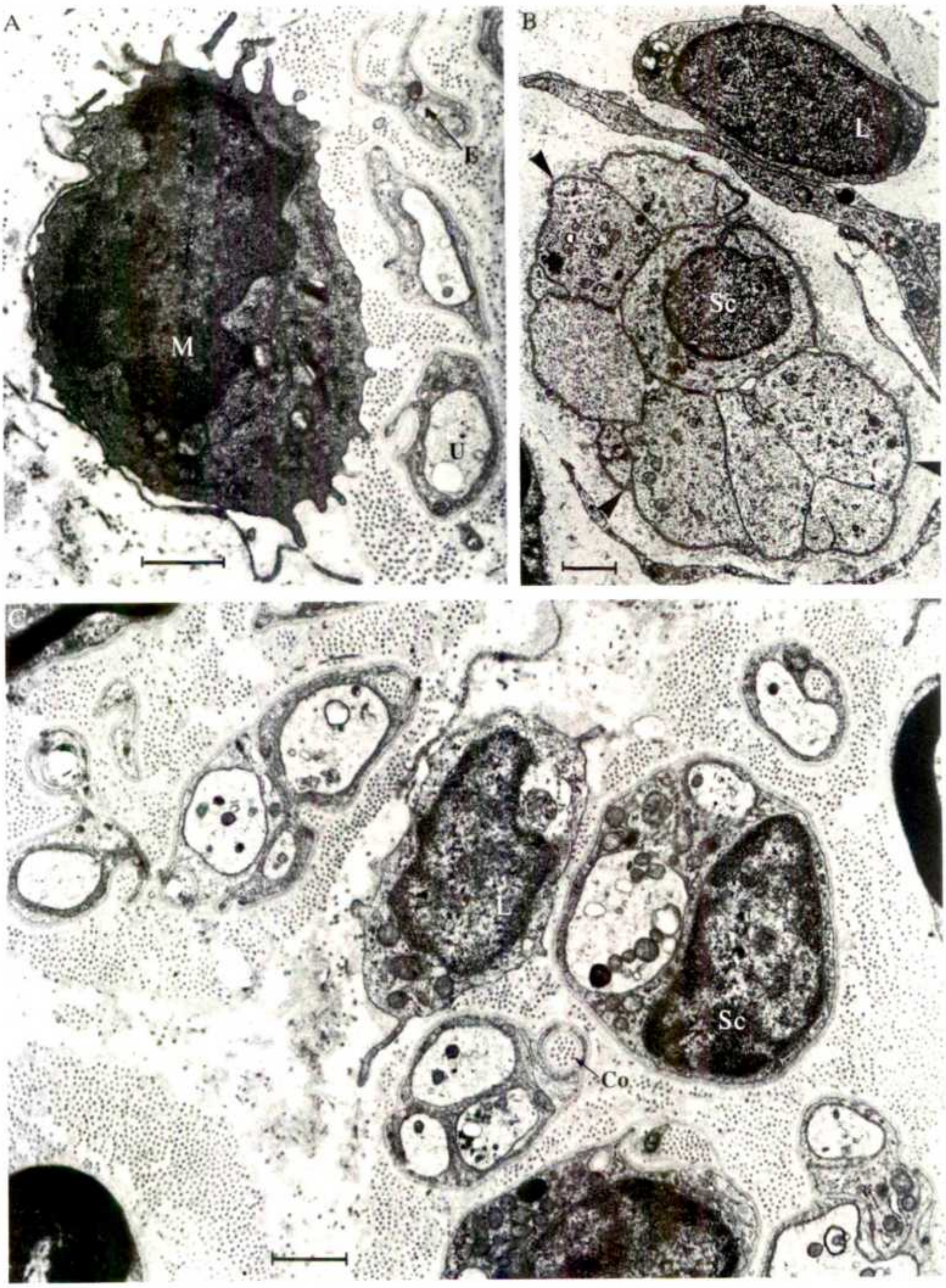

FIG. 5. Electron micrographs showing mononuclear cells within nerve fascicles. A, *Case 7*. Activated mononuclear cell (M) beside unmyelinated fibres (U) and an empty Schwann cell subunit (E). B, *Case 6*. A lymphocyte (L) is seen above denervated Büngner band (arrow heads) containing Schwann cell processes. C, *Case 7*. Lymphocyte (L) between unmyelinated fibres. Sc = Schwann cell nucleus. Co = collagen pocket. Bars = 1 μm.

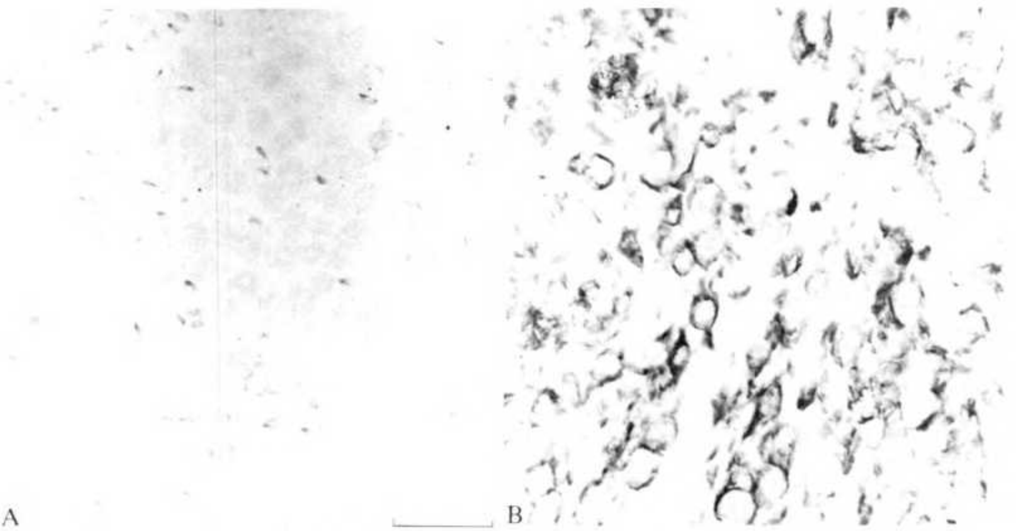

FIG. 6. Transverse sections of sural nerve immunostained with mouse monoclonal antibody to human common specificity Ia followed by peroxidase-conjugated goat antimouse IgG. A, normal control nerve. Staining represents endothelial and occasional mononuclear cells. B, sural nerve from *Case 2*. Note dense cell surface staining. Bar = 50 μm for A and B.

Thus quantification of the electron microscopy showed a significant loss of unmyelinated fibres, and a significant increase in collagen pockets, confirming the finding of axonal degeneration (Sharma and Thomas, 1975).

Immunoperoxidase staining. In healthy control nerves only very few lymphocytes or monocyte-macrophages were seen; these presumably accounted for the occasional Ia positive cells within the nerve fascicle (fig. 6A). Endothelial cells in control nerves were Ia positive; however, the density of this antigen in the endothelium was considerably less than that in SLE nerves (fig. 7). In control nerves with toxic neuropathy, M_1-positive cells or monocyte-macrophages were evident in proportion to the degree of axonal degeneration. Ia expression was likewise most dense within those nerves with the greatest monocyte-macrophage infiltrates. In 3 of the 6 patients (Cases 2, 6 and 7), there was perivascular infiltration with T lymphocytes, consisting of T11, T4 and T8 positive cells (fig. 8A). No significant difference in the numbers of T4 and T8 cells was found. Perivascular monocytes were found in Cases 2, 4 and 7. In Cases 2, 6 and 7 there were occasional T cells (T4 and T8) within the nerve fascicle. In Case 2 moderate numbers of T10-positive cells (activated lymphocytes) and macrophage-monocytes (M_1-positive cells) were present within the nerve fascicle (fig. 8B). A less dense infiltrate of macrophage-monocytes was present in Cases 6 and 7. In all nerves except that from Case 3, Ia-positive cells were present within the nerve fascicle (fig. 6B). Macrophage-monocytes presumably accounted for much of this staining since it was most dense within the nerve of Case 2, which also contained most M_1-positive cells, and more dense in Cases 6 and 7 than

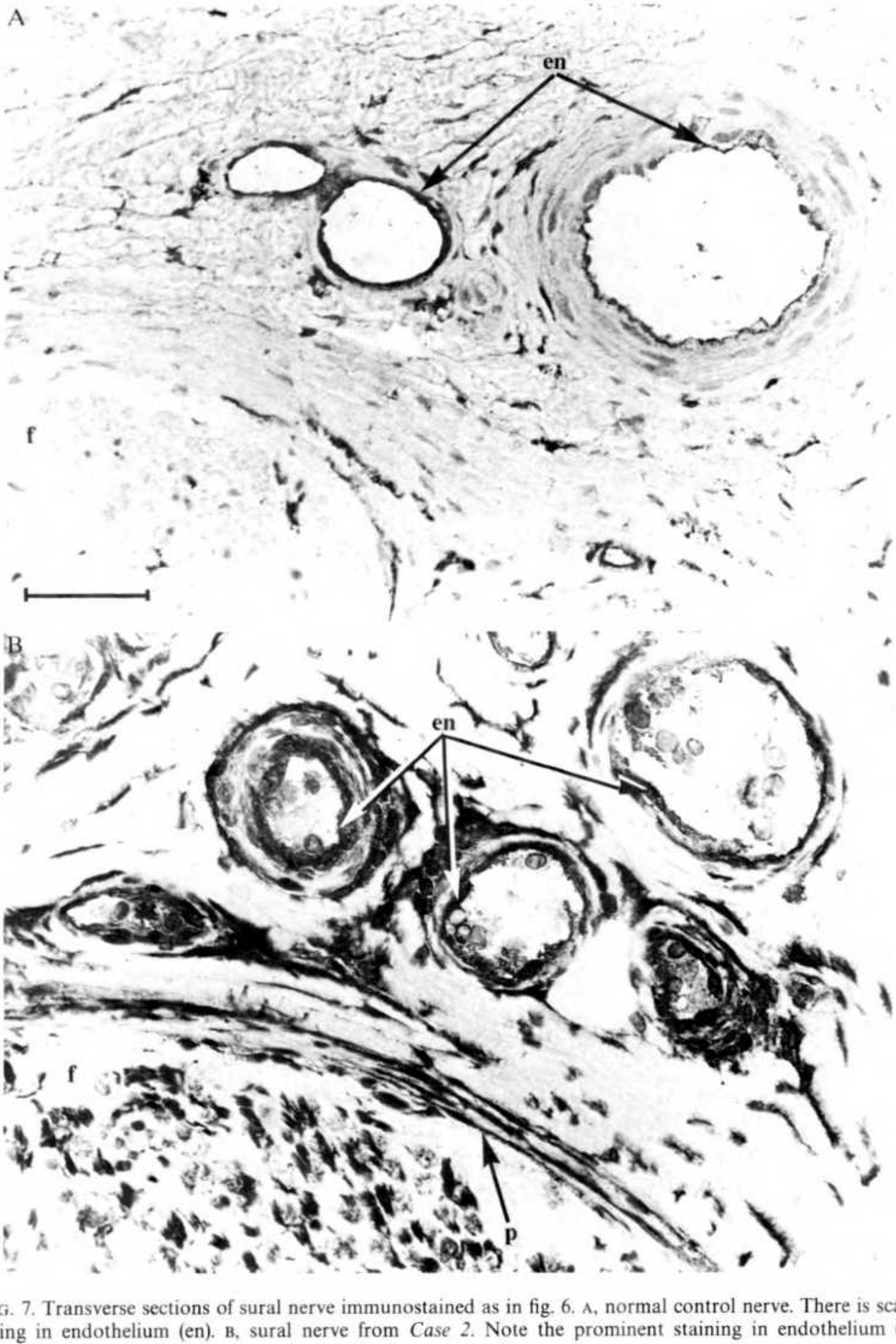

FIG. 7. Transverse sections of sural nerve immunostained as in fig. 6. A, normal control nerve. There is scanty staining in endothelium (en). B, sural nerve from *Case 2*. Note the prominent staining in endothelium (en), perineurium (p) and within the nerve fascicle (f). Bar = 50 μm for A and B.

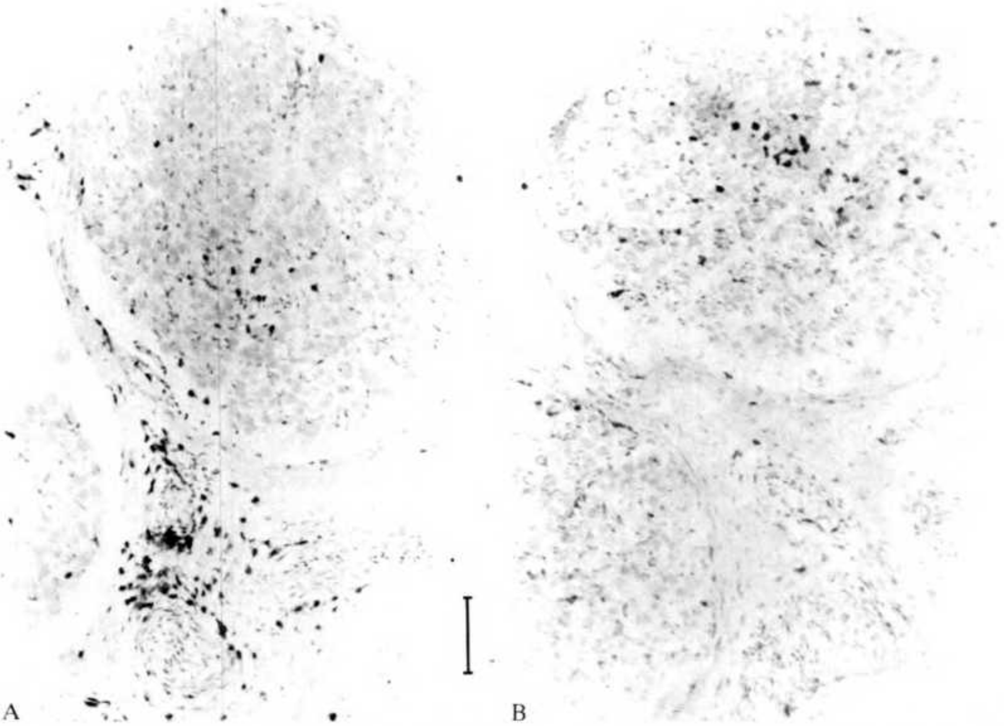

FIG. 8. Transverse sections of sural nerve from *Case 2*. A, immunostaining with mouse monoclonal antibody to T11 cells (all lymphocytes). B, immunostaining with mouse monoclonal antibody to monocyte-macrophages. In A lymphocytes are prominent in a perivascular distribution but are also present within the fascicle. In B moderate numbers of monocyte-macrophages are present within the nerve fascicle. Bar = 100 μm for A and B.

in Case 5. In all nerves, however, Ia-positive staining was more dense than could be accounted for by the contained mononuclear cells (figs. 6B, 8). In all nerves increased Ia staining was seen in endothelial cells (fig. 7) and within the perineurium and this staining was independent of the monocyte infiltration.

Immunofluorescence. Direct and indirect immunofluorescence was performed on control and patient nerves using antibodies to Ig, IgG, IgM, IgA and C3. In neither the control nerves nor those from the patients was there evidence of immunoglobulin or complement deposition within vessels or on nerve fibres.

DISCUSSION

Of the 7 patients studied, Cases 1–4 fulfilled the 1982 revised ARA criteria for the diagnosis of SLE (Tan *et al.*, 1982). The other 3 did not have all the usual clinical features but had high titres of antinuclear factor. They had an undifferentiated connective tissue disease clinically resembling SLE but not satisfying the ARA criteria. The only other likely diagnosis would be Sjögren's disease, but there were no clinical features of this condition. Kissel *et al.* (1985) reported 12 patients with vasculitis in the peripheral nerves but without the diagnosis of a well-defined collagen disease. However, they did not have high titres of antinuclear factor or the other laboratory evidence of immunological disorder seen in our patients.

All the patients had clinical and neurophysiological evidence of peripheral neuropathy for which extensive investigation revealed no cause other than SLE. The pattern of neuropathy in SLE is variable, but three types are recognized (Conn and Dyck, 1984). A progressive mixed sensorimotor type is the most common, and focal and multifocal neuropathies are well recognized. A rare neuronitis is characterized by more pronounced proximal than distal weakness, absent tendon reflexes, diminished sensation of posterior column type and elevated CSF protein content (Bailey *et al.*, 1956; Johnson and Richardson, 1968; Conn and Dyck, 1984). In all our cases the neuropathy was of gradual onset and of a chronic sensorimotor type but with predominantly sensory features. In 3 cases the initial distribution was asymmetric but a generalized symmetric peripheral neuropathy eventually developed. In no case were there clinical features of a multifocal neuropathy. Kissel *et al.* (1985) have also drawn attention to the frequency of a distal symmetric sensorimotor neuropathy in patients with vasculitis, in contrast to the classical multifocal pattern. In 4 cases, the neuropathy appeared after the other clinical manifestations of SLE, which is the usual sequence of clinical events (Conn and Dyck, 1984), but in some reported cases the neuropathy has been the presenting feature (Sidiq *et al.*, 1972; Bloch *et al.*, 1979; Sadeh *et al.*, 1980; Hughes *et al.*, 1982). In the other 3 cases the initial symptoms were those of a predominantly sensory neuropathy and laboratory evidence strongly suggestive of SLE was subsequently found. The response of the peripheral neuropathy to corticosteroid therapy was variable; in 2 patients with established SLE there was no improvement, but in 2 cases of probable SLE in which peripheral neuropathy was the presenting feature, improvement occurred.

The predominant pathological changes in the sural nerve biopsies were those of acute and chronic axonal degeneration with loss of myelinated and unmyelinated fibres. The blood vessels showed changes of intimal thickening and infiltration of round cells in and around the blood vessels. In previous reports axonal degeneration has been the most common pathological change in the nerve fibres (Bailey *et al.*, 1956; Scheinberg, 1956; Lewis, 1965; Johnson and Richardson, 1968; Hughes *et al.*, 1982), but chronic demyelinating pathology has also been reported (Rechthand *et al.*, 1984). Vasculitis is frequently present (Heptinstall and Sowry, 1952; Bailey *et al.*, 1956; Goldberg and Chitanondh, 1959; Hughes *et al.*, 1982; Kissel *et al.*, 1985), but in some cases there has been no evidence of vasculitis in the nerve (Scheinberg, 1956; Lewis, 1965; Siguier *et al.*, 1966; Johnson and Richardson, 1968; Rechthand *et al.*, 1984). Amorphous material in the endoneurium has been reported (Scheinberg, 1956; Tyrer, 1965; Hughes *et al.*, 1982).

Autonomic dysfunction in SLE has been reported in the Russian literature (Sablina, 1975; Tolubaev, 1979). There have also been case reports of autonomic dysfunction in autoimmune disease of uncertain categories (Edelman *et al.*, 1981;

Gudesblatt *et al.*, 1985). It has been suggested that acute pandysautonomia, occurring in isolation, may be due to an autoimmune disorder of the autonomic nervous system (Young *et al.*, 1975).

To investigate the possible role of immunological factors in the nerves of the patients studied, direct immunofluorescence and immunoperoxidase staining was performed. The monoclonal antibody immunoperoxidase staining demonstrated a lymphocyte infiltrate around vessels and within nerve fascicles of 3 patients. The infiltrate consisted of T11, T8 and T4-positive cells which are total, suppressor and helper T cells, respectively. No significant difference in the numbers of T4 and T8 cells was found. These immunocytochemical studies were confirmed by the electron microscope finding of infiltrating mononuclear cells. In the other patients inflammatory cells were not demonstrated within the fascicles, although a perivascular cell infiltrate of monocytes-macrophages was seen in a fourth patient. Rudick and Eskin (1983) demonstrated lymphocytes and plasma cells around vessels in the CNS in experimental SLE in mice. Immunoperoxidase staining also demonstrated Ia-positive cells endoneurially in all but 1 patient and in 3 patients moderate numbers of these cells were present within the fascicle. Much of this staining resulted from the presence of macrophage-monocytes and was most evident in those nerves showing most active axonal degeneration. Ia-positive cells were, however, more numerous than the total number of T cells and monocytes (figs 6, 8), which raises the possibility that another species of cell (e.g., Schwann cells) were expressing this antigen. The precise localization of cell surface antigens can be determined only by immuno-electron microscopy or by double labelling techniques. Nevertheless, the finding of cellular infiltrates within the nerve fascicles and in perivascular regions, and increased Class II antigen expression within the nerve fascicle, perineurium and in endothelial cells suggests that in some patients immunological factors as well as vasculitis play a role in the pathogenesis of the neuropathy.

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BOOK REVIEWS

Principles of Behavioral Neurology. Edited by M.-Marcel Mesulam. 1985. Pp. 405. Philadelphia: F. A. Davis. Price $68.75.

Specialization within a discipline is inevitable and desirable so long as it grows out of increased knowledge and technical expertise and does not reflect artificial demarcations along trade union lines. The subject matter of 'behavioural neurology' used to be the stock-in-trade of all neurologists (as still it should). Yet the emergence of this subdiscipline is totally legitimate and derives its impetus from a variety of directions. The first is the great expansion in experimental psychology as related to neurophysiology and the obvious application of the results to the clinical scene. The second is the enormous contribution that clinical neuropsychologists have made to the study of higher cerebral function in man on the basis of the investigation of patients with cerebral lesions. The third is the increasing possibility of being able to go some way towards approaching psychiatric disorders in terms of disordered cerebral function. These cross-disciplinary interactions have led to the emergence of the self-styled behavioural neurologists and the publication of an increasing number of texts. The book that is the subject of this review, edited by M.-Marcel Mesulam, is far and away the most interesting.

Mesulam's joint involvement in neuroanatomy and higher cerebral function provides the coordinating theme to the book, which is a much more cohesive enterprise than many multiauthor works. Mesulam himself is involved, alone or in collaboration, in four of the eleven chapters. He begins with a masterly account of 'behavioural neuroanatomy' in the first chapter, concentrating on hemisphere specialization, the association areas and the limbic cortex and, jointly with Sandra Weintraub, follows with a most useful account of mental state assessment in both young and ageing adults. He, again, is the author of the third chapter which is devoted to attention, confusional states and neglect. One of the most fascinating aspects of knowledge related to higher cerebral function to have expanded in recent years is the light that neglect syndromes throw on consciousness. The phenomenon of consciousness, standing at the focal point of human mental activity, is gradually escaping from the barren clutches of the philosopher and beginning to yield to neurophysiological analysis and experiment. Some aspects are emerging as a particular type of directed attention that can be investigated in the light of experimental studies in animals and the dynamic assessment of cerebral function in man.

Memory and amnesic syndromes are dealt with by Jean-Louis Signoret. This chapter perhaps gives less attention to relevant animal experimental studies than might have been expected. Aphasia and related disorders are covered in a succinct and comprehensive manner by Frank Benson and the late Norman Geschwind along orthodox Bostonian lines. The role of the right cerebral hemisphere in nonverbal communication and in the modulation of affect is considered in a short but important chapter by Elliott Ross. The relationship between disturbances of affect and the localization of cerebral lesions is still controversial, but it constitutes one area where the borderlines between neurology and psychiatry are showing an increasing degree of overlap. This has been apparent for some time in the phenomena of temporolimbic epilepsy, and the relevance of these to behavioural disturbances is the subject of a later chapter by Paul Spiers and others. Antonio Damasio deals with disorders of complex visual processing which, like aphasia and neglect syndromes, constitute an area in which cerebral lesions in man can be highly informative in providing insights into general concepts of cerebral processing. The final three chapters, by Robert Knight, Ruben Guv and Margaret Naeser, respectively, address electrophysiology (in particular, evoked potential studies), the imaging of regional brain physiology and quantitative CT studies in relation to behavioural neurology.

Although not comprehensive (the frontal lobes, for instance, are the victim of a relative neglect syndrome), *Principles of Behavioural Neurology* constitutes a very notable addition to this respected series of neurological monographs. Its expressed intention is to provide the background to some of the major areas of the subject and in this it succeeds admirably. The book is dedicated to the memory of Norman Geschwind, whose untimely death robbed clinical neurology of one of its most productive and interesting personalities, and who contributed so much to 'behavioural neurology'.

P. K. THOMAS

Subarachnoid Haemorrhage. By R. P. Sengupta and V. L. McAllister. 1986 Pp. 378. Berlin: Springer. Price £114 00.

In 1956 Sir John Walton published his classic monograph on subarachnoid haemorrhage in which he used a detailed review of 312 cases to present for the first time a contemporary description of all aspects of the condition including its outcome. It is therefore most appropriate that, thirty years later, it is he who provides the foreword to the excellent volume under review which has been produced by his former colleagues in Newcastle.

And what changes there are to record after thirty years! He writes that in those days 'angiography still had to be introduced as a routine method of radiological diagnosis in many centres in the UK'. Now our armoury includes finely detailed angiography, computerized x-ray and magnetic resonance imaging while microsurgery has been made possible by advances in anaesthesia. Sophisticated physiological monitoring systems are available and the clinician can draw on a wealth of epidemiological, clinical and experimental knowledge as he approaches each case.

Sengupta and McAllister have a vast clinical experience to qualify them for their task; 1000 cases of subarachnoid haemorrhage seen over a ten-year period provide the basis of the book while the surgical aspects are based on the first author's experience with his first 500 aneurysms. Five hundred consecutive cases of subarachnoid haemorrhage have been studied for their CT findings alone and all cases (524) seen between 1980 and 1983 analysed for aetiology.

The result is a remarkable distillation of knowledge and experience. The formidable array of statistics and tables are handled in a manner that is kind to the reader, the angiograms are well reproduced, the line drawings clear and the operative details helpful. Everything is well produced but the book works best when the Newcastle figures are being used as the basis from which the vast modern literature on the subject can be viewed in a proper perspective.

But in the end, what is the status of subarachnoid haemorrhage thirty years post-Walton? Despite all the accumulated knowledge that is so well described here, it still remains a disease whose incidence and mortality has been affected less than perhaps we would like to imagine. And the fact that this often goes unrecognized is due in part to the technical aspects (and temptations) of aneurysm surgery that make up much of this book. Neurosurgeons enjoy clipping aneurysms. It seems to be one of the natural reasons for which neurosurgeons were created. When they see an angiogram that reveals an aneurysm as the source of their patient's subarachnoid haemorrhage, their fingers start twitching in excited foreplay. Then, in what is perhaps a subconscious defence mechanism, they collude in giving the impression that, because that aneurysm has now been clipped, all must be well with the subject as a whole. Personal series so small that the cases cannot be divided by aneurysm site are frequently presented in the literature (Sengupta and McAllister escape this charge easily) and quality of survival is often dealt with in a cursory fashion (Sengupta and McAllister are not so innocent here. Forty pages of their book are devoted to the Basic Principles of Surgical Treatment of Intracranial Aneurysms, twenty lines to The Quality of Survival). Meanwhile cerebral arterial vasospasm remains as mysterious and dangerous a condition as when it was first demonstrated angiographically in 1951.

For many reasons it can be difficult for neurosurgeons to heed the grey epidemiological voice that suggests, as Kassell and Drake are quoted as showing in the chapter on Future Developments, that of the 28 000 patients expected to have a subarachnoid haemorrhage each year in the US, just 9000 are likely to survive without disability. Only when missed diagnoses have been eliminated by better education of physicians and some way of predicting risk before haemorrhage occurs, will more than the present 64% of patients survive to reach a neurosurgical centre. And only when their early management, both medical and surgical, has been improved will more than half of them avoid the episodes of rebleeding and ischaemia, together with the medical and surgical complications that still prevent them from enjoying a favourable outcome.

Overall an excellent book and one to be recommended.

R. D. HAYWARD

Recent Advances in Epilepsy 3. Edited by T. A. Pedley and B. S. Meldrum. 1986. Pp. 315. Edinburgh: Churchill Livingstone. Price £38.00.

This is the third book in three years in the *Recent Advances in Epilepsy* series and the format and style of the previous editions are followed closely. The book is composed of 14 chapters, each written by an authority in the field, and each intended to be a more or less comprehensive review of the topic; as before, there is a mixture of basic scientific (relegated to a single chapter in this volume), clinical and therapeutic subjects; and as before the editing has been strict and the book has a remarkable coherence, which most multiauthored efforts lack. One does, however, sense that the formula for the series is beginning to tire, the choice of subjects is generally less interesting than in previous editions and although individual contribution are bound to vary in quality, one or two in this book are well below standard. Basic science is represented by a good chapter (Ribak) on the neurocytology and chemistry of focal epilepsy, in which much of the author's own work—previously published only in specialist journals—is presented, and much was new to the reviewer. The evidence given for the preferential loss of GABAergic neurons at epileptic foci is particularly intriguing and has obvious implications to our understanding of the whole process of the development of epilepsy. The best clinical chapter is a superb review of the Aicardi syndrome (Chevrie and Aicardi) which will surely be a standard reference on this subject. The chapter on the interrelationships between sleep and epilepsy (Baldy-Moulinier) is also an original contribution taking us a step forward from Janz's reviews, now some decades old. The chapter on seizures of frontal lobe origin (Quesney) is timely, as our understanding of this subject has been considerably increased with the introduction of newer electrophysiological techniques. The differentiation of frontal and temporal lobe seizures has become an important clinical issue, and the clinical presentation and the surgical treatment of frontal seizures is well reviewed, with emphasis on extensive Montreal experience. The chapter is supported by well chosen clinical vignettes and EEG illustrations, but the emphasis on supraorbital electrode placement is perhaps a little unbalanced. There are good chapters on the progressive myoclonic epilepsies (Berkovic and Andermann) and ambulatory EEG monitoring (Ebersole and Bridgers) although these are both subjects which have been extensively reviewed elsewhere. This is perhaps my main criticism of the book, that for many of the chosen subjects, equally good review material is readily available elsewhere and, unlike the two previous volumes, there is little original work presented. The chapter on psychomotor seizures of hippocampal-amygdaloid origin (Wieser), for instance, although well done, reiterates rather wearily much of the author's very well-known work. The chapter on the genetics of epilepsy (Hauser and Anderson) tackles a difficult subject, but goes over old ground and is sadly rather disappointing. The other clinical chapters are interesting, but contain much which is uncritical or superficial. There are three chapters devoted to therapy. The update on ethosuximide (Fromm and Crumrine) is useful, but that on the barbiturates (Pritchard and Mattson) less so, and Schmidt surely had an impossible task in reviewing the toxicity of antiepileptic drugs in 20 pages. All in all, this is the least successful of the three books of this very useful series. It nevertheless deserves a place in any epilepsy library, although at £38 it is not cheap, and expense is a matter about which the publisher should be taken to task.

SIMON SHORVON

Headache. By Richard Peatfield. 1986. Pp. 178. Berlin: Springer. Price £36.00.

This book deals with the basic mechanisms, diagnosis and investigation of headache. In the first sections the classification of headache, epidemiology, history taking, clinical examination and investigations for such patients are discussed. The main organic causes of headache are listed, they are short but informative. The main part of the book is devoted to migraine. Surprisingly very little attention is given to the headaches which the author refers to as 'those called tension headache', although in the table on page 168 he gives the approximate prevalence per million as over 600 000 for nonspecific 'tension headaches' and 480 000 for classical and common migraine. The prevalence seems rather high for both migraine and tension headache. In this book the author uses the term functional to describe pathophysiological disturbances and under this term syndromes such as drug-induced headache, coital headache and exertional headache are included. This use of the term functional, although he cites Charcot and Hughlings Jackson as a source, may cause some confusion to the reader. The sections on the clinical features of migraine and other headaches are clear and well written, as is the section on cluster headache.

Dr Peatfield addresses the problem as to whether migraine is a neural or vascular disorder but appears to come to no definite conclusion, except that attacks of headache involve disturbances both of the CNS and the cerebral and cranial vasculature. In Chapter 5 he concludes that there is very little direct evidence to support Wolffe's original conception that the aura symptoms of classical migraine are due to spasm of cerebral blood vessels and that the vasodilatation of the headache is caused by secondary reactive hyperaemia.

In his classification, however, migraine is listed as a vascular headache and he considers that the evidence that headache is due to painful vasodilatation of extracranial vessels is compelling although the intensity of the pain does not correlate with the degree of vasodilatation and that therefore some other factor is contributing to the 'sterile inflammatory process' that appears to be taking place around the arteries. He also appears to support the theory that the spreading depression of Leão plays an important part in the pathophysiology of migraine, basing this mainly on the blood flow studies of Olesen and his colleagues. The main objection to this theory is that spreading depression has rarely, if ever, been observed in the human cortex.

The sections on the treatment of acute headache and the prevention of headaches provide a great deal of information and references are made to most of the key publications on the relevant subject, but for the less experienced, very little direction is given as to which drug and what dose should be used, although he does suggest that propranolol and piyzotifen are the drugs of choice in migraine. In the section on acute headaches very little difference is made between the treatment of migraine and other types of headache, although it is probable that metoclopramide, domperidone and ergotamine tartrate and its derivatives are only beneficial in migraine. The section on miscellaneous treatment gives a good idea of some of the alternative treatments available and their possible value.

This is an interesting and instructive book on headache and should be read by all those interested in this field.

MARCIA WILKINSON

Basic Neurology. By George David Perkin. 1986. Pp. 327. Weinheim: Edition Medizin. Price DM 74.00.

Most clinical neurologists with responsibilities for teaching undergraduates feel able to criticize the several available texts. These are considered to be too long or too short, too didactic or too scientifically orientated, too encyclopaedic or too superficial, too expensive or too shoddy, etc., etc. Each book is really a penetrating Rorschach reflecting the writer's disposition as well as his clinical interests and experience. While most of us cavil from the armchair, few show the sustained application and determination required to compose their own opus Fortunately, among the latter is David Perkin. The format of his book is traditional—clinical method, common neurological syndromes, specific neurological disorders, neurology and general medical disorders, relationship to psychiatry and the intriguing final section concerning the undiagnosed patient. The Appendix refers to the nubbin of his experience—an analysis of 4,000 successive personally-seen referrals. It is this that gives the book its distinctive quality of topicality and comprehensiveness appreciative to the needs of an undergraduate audience. For these refreshing reasons *Basic Neurology* is warmly recommended to teachers and their students.

Gerald Stern

Orthostatic Hypotension. By Irwin J. Schatz. 1986. Pp. 146. Philadelphia: F. A. Davis. Price £37.50.

Dr Schatz has impeccable credentials for writing a monograph on orthostatic hypotension because his first paper appeared in 1963, a mere three years after Shy and Drager first described the findings of autonomic failure in two patients. Since then Dr Schatz has kept an expert interest in the subject, in particular with respect to treatment with steroids.

This has ensured that his monograph is topical and soundly based on circulatory physiology without, understandably, straying into neurological territory. There have been so many advances in the past ten years that a review of this kind is particularly helpful to the general physician. There are only a few statements that I would hesitate to endorse fully. I think the postural hypotension in anorexia nervosa is as likely to be the result of a hypothalamic lesion for which there is evidence, as simply a lack of 'venous pump' from atrophic peripheral musculature. He still supports rather more strongly than I feel is justified by the evidence, the Sharpey-Schafer view that in diabetics an afferent lesion is common. He also implies that bladder involvement is commoner in patients with what he describes as idiopathic orthostatic hypotension than is true in our experience. As with all American writers, the term idiopathic orthostatic hypotension lingers to complicate the modern nomenclature, especially as it is sometimes used of patients with minor neurological symptoms who are therefore probably suffering from either superadded parkinsonism or multiple system atrophy.

There are some interesting new presenting symptoms which are discussed such as angina due to orthostatic hypotension. He is a little hard on the usefulness of the tilt table which tests cardiovascular reflexes more simply than the act of standing. Though standing is clearly more relevant, it has complex effects due to skeletal muscle contraction which, over the first thirty seconds of standing, are difficult to interpret. He describes several cases to illustrate usual presentations, although the patient aged 32 with unsteadiness since the age of 18 must be regarded as very atypical of multiple system atrophy with progressive autonomic failure.

This book can be recommended as an authoritative review for medical students and physicians who require a practical physician's approach to diagnosis and management in a field where the complexities of diagnosis and the options for treatment are frequently misunderstood.

Roger Bannister

Recent Achievements in Restorative Neurology. Volume 2. **Progressive Neuromuscular Disease.** Edited by M. R. Dimitrijevic, B. A. Kakulus and G. Vrbova. 1986. Pp. 360. Basel: Karger. Price DM 335.00.

This book is a record of the Proceedings of the Second Symposium on 'Recent Achievements in Restorative Neurology' held in the USA in October 1984. A glance at the list of contributors suggests that this must have been a stimulating and exciting symposium for the participants, but two years and the 'book' format do little to transmit this to the reader, who must lurch through remarkable juxtapositions of detailed basic experiments and clinical review. The intention, admirable in concept, is to draw together clinical realities of management and the experimental basis for such activities.

The first section is notable for a clear account of the management of Duchenne dystrophy in Western Australia (Miller and Kakulas) and this is preceded by a remarkably brief chapter (barely two pages) on the management of scoliosis in neuromuscular disease (Dickson). The section on Motor Unit Physiology/Posture/Gait somewhat incongruously starts with an experimental paper from Dubowitz's group on low frequency stimulation of muscle in Duchenne dystrophy and continues with interesting papers on various aspects of gait analysis by Dimitrijevic, Larsson, Grimby and others—in particular, a discussion on the alteration of the pattern of leg muscle activation in weak children by Dietz. The following section (labelled Pathophysiology) contains clear reviews of methods for assessing muscle strength and performance (Henriksson) and muscle fatigue (Jones and Edwards). Also to be found here is a chapter on computed tomography of muscle (Serratrice) but I was left uncertain as to the light this shed on Pathophysiology. Two chapters cover Pharmacology in a descriptive rather than experimental manner. The last section of this book concerns 'Neurobiology'. This includes chapters (in succession) on molecular genetics by Harper, trophic factors and motor neuron development by Appel and experimental work on developmental synapse reorganization by Vrbova. Subsections on the phenotypic expression of muscle fibres (including contributions from Stålberg, Hilton Brown, Pette and others) and muscle development and maturity (Fidzianska, Eccles and Nix) follow.

Inevitably much of the material presented has been published in fuller form elsewhere and some of the chapters even maintain the layout of scientific papers. I found the section headings of the book artificial and slightly inappropriate. Clinicians seeking an authoritative review on the effects of chronic nerve stimulation in animal and clinical work, for example, will not find it here but will need to read individual contributions in several different sections. On the other hand muscle fatigue, strength measurements and gene mapping in Duchenne dystrophy are rather well reviewed.

These criticisms reflect the nature of the subject as much as anything and illustrate the fact that what makes an illuminating symposium does not necessarily make a good read. Despite the fact that many distinguished clinicians and scientists have contributed to this book, I find it difficult to know which groups of people involved in neuromuscular research might enjoy reading it—especially at a purchase price of over £100.

C. M. Wiles

Neuropsychological Assessment of Neuropsychiatric Disorders. Edited by Igor Grant and Kenneth M. Adams. 1986. Pp. 536. New York and Oxford: Oxford University Press. Price £40.00.

This edited text is one of a number which are now appearing in the very rapidly advancing area of clinical neuropsychology. The two editors (Igor Grant, a psychiatrist and Ken Adams, a psychologist) have brought together a 'who's who' list of contributors to address some of the central questions in clinical neuropsychology. The title of the text refers to 'neuropsychiatric disorders', but the editors have quite rightly interpreted 'neuropsychiatric' very widely, allowing them to include contributions covering a wide range of conditions including schizophrenia, dementia, depression, Parkinson's disease, etc.

The text is in two parts. The first incorporates 5 chapters dealing with methods of assessment, and the second consists of 15 chapters dealing with specific problems. The 5 chapters in part 1 together comprise an unusually complete discussion of the problems involved in neuropsychological assessment. Almost all approaches are covered, ranging from the use of a comprehensive test battery (Chapter 1), to a theory-driven analytic approach (Chapter 2), and a clinically-driven individual patient orientated approach (Chapter 4). This section alone almost makes the book worth buying.

The second section incorporates chapters dealing with a wide variety of disorders, and as such it is perhaps slightly more uneven in tone, with chapters of varying length, complexity, and completeness of coverage. Nevertheless, overall this section is extremely valuable, and two of the chapters (6 and 7) dealing respectively with factors such as age, education, and sex on neuropsychological test performance and applied neuropsychology in a psychiatric setting, are especially valuable containing material which is often inaccessible to the neuropsychological clinician, yet which is fundamental for carrying out high quality neuropsychological work.

If one wanted to carp, it could be pointed out that the text does not contain a by now mandatory introduction to neuroscience, and that it is devoted largely to the problems of neuropsychiatric disorders in adults rather than children. These are not important criticisms Introductions to neuroscience can be found in plenty elsewhere, and paediatric neuropsychiatric disorders are sufficiently different and specialized to warrant a separate text.

At £40.00 this book is very good value for money. It contains information that will certainly be of interest to psychiatrist and psychologists, but many of the chapters will be of interest to other medical practitioners (e.g., neurologists), and to a wide variety of the clinical specialists (speech therapists, etc.) working with brain-injured patients. It is highly recommended.

NEIL BROOKS

Experimental Techniques in Human Neuropsychology. By H. J. Hannay. 1986. Pp. 593. Oxford: Oxford University Press. Price £50.00.

The need to evaluate and take stock of the various methods used in neuropsychological research is underscored by the recent emergence of special journal issues and edited volumes devoted to these concerns. *Experimental Techniques in Neuropsychology*, edited by H. J. Hannay, is the best collection of this kind to date. The chapters, representing a broad spectrum of neuropsychological methods, in general adhere thoughtfully to the goal of outlining and evaluating the important features of their respective methodologies. The purpose of a text of this kind is twofold: to aid in the understanding and evaluation of research based on methods with which a reader may be unfamiliar, and to provide a source of information about experimental design. When writing about methodology an author's theoretical biases or beliefs can come into tension with the demand for objectivity. Although the authors in this volume vary considerably in their handling of this implicit tension, the text as a whole can be applauded for its balanced and thorough coverage of many techniques used in neuropsychological investigation.

The chapters on dichotic listening (Springer), tachistoscopy (McKeever), lateral eye movements and the dual task paradigm (Hiscock) present the theoretical and empirical bases of the methods, overview the major findings from these paradigms in a concise and judicial manner, and consider probable causes of variability associated with them. Useful discussions of the practical considerations that arise with these methods are also provided. Fennell's chapter on handedness takes a similar approach and compares the content and reliability of various handedness inventories. In a thorough chapter on psychophysical methodology, Hannay offers a clear introduction to the associated theory and highlights the virtues and difficulties of this under-used methodology. Malone's chapter on intersensory integration calls attention to a line of research in neuropsychology which is deserving of further investigation. In a highly technical and nonpsychological chapter, DeBacher covers electromyography. Varney introduces the reader to valuable clinical insights relevant to the study of somaethesis but does not deal sufficiently with the interpretation of results from the various methods he reviews.

Gevins presents a somewhat one-sided and conservative approach to electrophysiological research. In an informative and technically sophisticated chapter he delineates major methodological pitfalls encountered when attributing EEG and ERP differences to cognitive factors. The message is valuable but leaves the impression that little has been learned from this approach. In addition to a lucid tutorial on the ERP, Squires and Ollo help to counteract Gevins' pessimism through an overview of the clinical and research applications of the ERP which introduces some of the important questions that can be addressed through creative implementation of these measures. The chapter on blood flow research (Risberg) focuses on the xenon inhalation technique to the exclusion of other approaches. It concentrates on research from normal populations which offer the necessary framework with which to interpret clinical findings. However, the chapter omits any discussion of the promising and intriguing results from the use of this methodology to study the topography of functional lesions that can accompany focal brain damage.

The chapters on attention (Sheer and Schrock) and learning and memory (Levin) delineate the typical procedures used to study these cognitive functions. The attention chapter is weak due to its failure to examine the fruitful integration that has taken place between cognitive experimental psychology and neuropsychology, particularly in reference to the effects of focal brain lesions on attentional orienting. The chapter on memory could be improved by a deeper analysis of the use of dissociations between memory measures to make inferences about mnemonic processes

The contribution of Martin and Caramazza stands out because of its sophisticated presentation of the interplay between theory and methodology in neurolinguistic research. The authors are unique in this collection in their discussion of the broader goals in neuropsychology and the impact of this larger agenda on the interpretation of research on clinical and normal populations.

The text lacks a chapter on reaction time and on the computational approach in neuropsychology. Such issues are addressed in other volumes which could be used to supplement the present text. The reader of this volume is sure to find it useful, regardless of their familiarity with the field, and the book will be a valuable resource in the education of future neuropsychologists.

P. A. Reuter-Lorenz

Positron Emission Tomography. Edited by Martin Reivich and Abass Alavi. 1985. Pp. 478. London and New York: Alan Liss. Price £61.00.

Positron Emission Tomography is the third book on functional brain imaging that this reviewer has been invited to comment on for *Brain*. It is the best of the three. The editors have ensured that the whole field of positron emission tomography (PET) is covered—this includes physics, radiochemistry, reconstruction algorithms and tracer methodologies, so there is much here to daunt the reader whose higher education was confined to the medical sciences. Functional images of the brain appear infrequently, and when they do they are of rather poor quality. The reader is expected to concentrate on a text liberally illuminated with tables, mathematical expressions and illustrative line drawings. This earnest approach is not for the casual browser, but it serves the subject well. Anecdotal images are fun, especially when reproduced in Disney colour schemes, but they do not win respect, and expensive PET research will ultimately be judged on its quantitative results.

The contributors come from many of the major centres involved in clinical research with PET. The Los Angeles group at UCLA are conspicuous by their absence, but this is explained by the recent publication of their rival to this volume. The book starts with a chapter on autoradiography. PET, which is the in vivo equivalent of autoradiography, depends on quantitative tracer techniques, and many of the established and proposed methodologies have been, or will be, formulated after research and validation with autoradiographic studies on animals. Sokoloff's comprehensive review is, therefore, a useful introduction before the reader becomes immersed in the physics, the chemistry and the mathematics of PET research. PET instrumentation is presented in terms of basic principles, which will be of interest to the nonspecialist. In contrast, the chapter on positron-emitting radiotracers is an inventory of compounds of biological interest that can be labelled by the radiochemists. It is well referenced and is clearly directed at workers in the field as a list of goods in stock. The major strength of the book is the amount of space devoted to the presentation of many of the tracer techniques in current use—those designed to measure regional glucose metabolism, oxygen consumption, blood flow and volume, protein synthesis, pH, and simple pharmacokinetics. All in vivo tracer models, whether they describe the fate of the labelled compound in terms of one compartment (the oxygen-15 steady-state technique) or three (deoxyglucose as tracer to measure glucose metabolism) incorporate simplifications, assumptions and constraints that introduce small errors at best, and may frankly mislead in diseased brain. Therefore it is appropriate the tracer methodologies should occupy one-third of this book. One aspect not touched upon, although it is the current major preoccupation in PET research, is the use of labelled precursors and ligands to investigate neurotransmitter synthesis and turnover, and neuroreceptor density, specificity and distribution. Whether it will ever be possible to quantitate the concentration of a specific neuroreceptor in a brain region using in vivo studies on man remains to be seen, but the book suffers for want of a chapter on this potentially most rewarding area of PET research.

This omission aside, the principles and methods are generally well covered. The authors of the chapters on clinical results have produced contributions of a more variable standard. Broadly speaking there are those who like looking at images and others who prefer to contemplate numbers. The decision about which temporal lobe is the source of seizure activity (it is hypometabolic interictally and hypermetabolic ictally) or the grade of a brain tumour (the hotter the spot on a deoxyglucose scan the more malignant the tumour), is best arrived at by the standard technique of the radiologist, that is by eyeing the relative regional densities of a transaxial reconstruction of the data on an x-ray plate or video screen. This done, PET becomes an expensive branch of nuclear medicine with potential for influencing individual patient management. In contrast, the effects of ageing and dementia on regional cerebral metabolism can only be revealed by statistical analysis of quantitative studies on relatively large populations. Satisfyingly, the numbers prove what you always knew—for the more senior that nothing has changed since your twenty-first birthday, and for those still young that the increasingly dotty decisions emanating from older colleagues who occupy more elevated positions in the hierarchy are only a reflection of plunging cerebral metabolism as the plaques and tangles accumulate.

Inevitably the quality of the chapters on clinical PET research is in direct proportion to the achievements to date. Cerebrovascular disease is well served by a number of contributors, and to consider the consequences of ischaemic disease in terms of supply and demand (blood flow and oxygen and glucose metabolism) is getting at one of the roots of the problem. The chapter on psychiatric research is altogether much less substantial, but this reflects the paucity of hypotheses about the aetiology of mental illness. The expressed vague hope that more and better radiotracers will uncover the mysteries of schizophrenia carries little conviction. PET is like any other technique capable of generating vast quantities of data very rapidly—the less structured the question put in, the more incomprehensible and irrelevant the numbers that come out.

Therefore if the reader finds the section on clinical results a little thin, it would be wrong to blame the technique. There is plenty in this book to reveal the potentials of emission tomography, and the effort required to develop and refine a tracer technique until precision is achieved. Then the vital ingredient is some inspired fantasy, and the ability to test intuition with a direct question. Physicists, radiochemists and neuroscientists can then set to, to explore the hypothesis in vivo in man. As this will all take time, the next edition of this book should be scheduled to appear in 1996. We are now well served with books on PET for the time being.

RICHARD WISE

Neuroendocrine Perspectives. Volume 5. Edited by Eugenio E. Muller and Robert M. MacLeod. 1986. Pp. 357. Amsterdam: Elsevier. Price Dfl. 205.00.

The fifth volume of the series *Neuroendocrine Perspectives* consists of many of the papers presented at the 2nd Meeting of the European Neuroendocrine Association in Milan in October 1985. The theme of this meeting was Hypophysiotrophic Peptides in Basic and Clinical Neuroendocrinology. The papers are all in variable, camera-ready form but publication has not been as rapid as one might have hoped (nine months) so that most of the data presented have now been published.

In view of the attempt at rapid publication, there has been no obvious editorial control. What the editors have done is to bring together related papers into 6 sections of the book. The first section covers 'Basic Aspects of Hypophysiotrophic Peptides'. This includes several well-written articles covering the role of growth hormone releasing factor (Wylie Vale *et al.*), the characteristics of neurohormone secretion into portal blood (George Fink), the interaction between signalling systems on pituitary function (Kordon and Enjalbert), and receptor and postreceptor effects of hypothalamic peptides on pituitary cells (MacLeod *et al.*).

The second section on clinical aspects of hypophysiotrophic peptides is rather less satisfactory. We are only at a very early stage in our understanding of the clinical value of the administration of these neuropeptides and it is certainly important to assess the results found by different groups. However, I found that the 9 chapters in this section presented little new data and were rather repetitive. The overview chapter by Seymour Reichlin, however, provides a clear summary of the diagnostic and therapeutic potential of these peptides and also presents interesting data on the endocrine consequences of intrathecal TRH given to patients with motor neuron disease.

The next section covers a much neglected area of endocrinology—the effects of ageing. The most notable chapter in this section is by Joseph Meites, which provides elegant evidence that disruption of hypothalamic function with age could explain many aspects of declining reproductive function, mammary and pituitary tumours, and changes in muscle protein synthesis.

No symposium on the neuroendocrine axis can ignore the role of recombinant DNA techniques. This section of the book includes a chapter on vasopressin and oxytocin gene expression by Ivell and Richter, a fascinating description of how expression cloning was used to elucidate the structure of the TRH precursor (Goodman *et al.*), and further studies on prolactin and human calcitonin/α CGRP gene expression.

The two final sections cover the role of neurotransmitters and intracellular signalling. These include several disparate chapters with notable contributions by Petersen and Barraclough on hypothalamic opiate interactions in the regulation of LH and prolactin, and a description of the use of affinity labelling of growth hormone releasing factor receptors by Velıçelebi *et al.*

The publication of meetings proceedings always presents editors with major problems and this is no exception. The book certainly contains some chapters of great interest. However, at $76 (price in UK £s not quoted), few people will find either the detail or breadth of coverage of this volume sufficient to warrant its purchase.

STAFFORD LIGHTMAN

Brain Growth. Edited by H.-J. Ketschmann. 1986. Pp. 140. *Bibliotheca Anatomica* No. 28. Basel: Karger. Price DM 168.00.

This slim volume consists of six papers on morphological aspects of pre- and postnatal brain growth. The first three deal with normal human brain growth and are based primarily on the Yakovlev collection of material in Washington, DC. The first paper considers global brain growth as portrayed by changing brain weight, the second, hippocampal growth assessed by volumetric change, and the third, differential growth of various brain parts, also volumetrically determined. In each the data is comprehensively presented in tables and the statistical analyses are summarized graphically. Assimilation of these primary data is hard going but the discussions that follow are of more general interest. For example, it is pointed out that tissue shrinkage following fixation is inversely related to the age of the brain. Thus it is comforting to know that the reported loss of nerve cells after the age of 50 years may be more apparent than real as the septuagenarian brain shrinks less than the 50-year-old, so its neurons are less numerous per unit volume of fixed tissue.

The fourth paper is a detailed study of the development of fissuration and myelination in the cerebellum of mice with trisomy 19. The major morphological abnormalities associated with this condition were a general retardation of axon growth and myelination with an even greater lag in the development of fissures. The last two papers consider changes in the cerebellum of ageing rats assessed by changes in weight and cell number. The results give no neat insight into cerebellar ageing but reveal the difficulty in interpreting small variations in such gross parameters in a complex tissue.

This volume will be of most interest to neurologists and neuroscientists directly involved in morphometric studies of brain growth.

I. H. M. SMART

ANNOUNCEMENTS

American Association for Electromyography and Electrodiagnosis

The AMEE is sponsoring continuing medical education courses in San Antonio, Texas. For information, contact Ella M. Van Laningham, AMEE Executive Director, 732 Marquette Bank Building, Rochester, MN 55904, USA.

International Symposium on Spinal Analgesia: Basic Concepts and Clinical Application

This Symposium will be held on August 9-12, 1987, at the Technical University Medical Center, Munich, West Germany. It is an official satellite symposium to the Fifth World Congress on pain (Hamburg, August 2-7, 1987). Further information may be obtained from Professor A. Herz, Max-Planck-Institut für Psychiatrie, Am Klopferspitz 18A, D-8033 Planegg Martinsried, FRG, or Professor A. Struppler and Dr A. Weindl, Department of Neurology, Technical University, Möhlstrasse 28, D-8000 München 80, FRG.

Blood Vessel Imaging Using Ultrasound Techniques

A three-day residential course and workshop will be held at the Dolphin Hotel, Southampton, on May 11-13, 1987, on the application of echo and Doppler ultrasound techniques to the investigation of the cardiovasculature. Further information may be obtained from K. N. Humphries, Blood Imaging Course, 5 Mossleigh Avenue, Rownhams, Southampton SO1 8FU, UK.

Second Mainz Conference on Different Approaches to the Motor Unit

This will be held on May 16-17, 1987. It will be preceded by a course on single fibre EMG to be held on May 15 For information, contact Professor W. Nix, Department of Neurology, University Clinics, Langenbeckstrasse 1, 6500 Mainz, FRG. Telephone (06131) 17-3271.

Molecular Aspects of Diseases of Motor Function

This meeting will be held on September 14-15, 1987, in Manchester, UK. The programme will include neuromuscular disorders, neurovirology and neurological syndromes, and movement disorders. For information, contact Dr A. J. Cross, Astra Neuroscience Research Unit, 1 Wakefield Street, London WC1N 1PJ.

Brain Travelling Fellowships

Applications are invited for two travelling fellowships enabling young postgraduates seeking a training in the neurosciences to spend up to 12 months in an approved academic department. One fellowship will be restricted to foreign graduates wishing to spend time in a UK department, and one to UK graduates wishing to travel abroad

Applications should include a curriculum vitae, a letter of support from the applicant's current head of department or consultant and an agreement in principle from the proposed host department. Travel expenses and a salary of up to senior registrar (UK level) available according to seniority.

Applications (*six copies*) to Dr Alastair Compston, University of Wales College of Medicine, Department of Medicine, Heath Park, Cardiff CF4 4XN, by September 1, 1987.

Travel Grants
For Young Neuroscientists

The Guarantors of *Brain* are prepared to consider applications for contributions towards travel costs from neuroscientists under the age of 40 working in the United Kingdom.

1. The primary purpose of such grants is to facilitate short visits to laboratories or departments of particular relevance to the applicant's research. Applications cannot be entertained without the following documents.
   (a) an abbreviated curriculum vitae and a list of any relevant publications;
   (b) statement of age and post currently held;
   (c) a concise account of the purpose of the proposed visit;
   (d) a recommendation from the head of department (where appropriate);
   (e) a letter of acceptance from the department to be visited;
   (f) a statement of costs likely to be incurred, and of other applications for funds that have been made. Advantage should always to taken of reduced air fares when available.
2. Applications will also be considered for contributions to the cost of attending specialized symposia of particular importance to the applicant's research. Documents as in (a), (b), (c), (d) and (f) above should be submitted at least three months before the date of the meeting, accompanied by a statement of what other applications for financial aid have been made and of any contributions by the symposium organization.
3. Only exceptionally will applications for assistance to attend larger international congresses be entertained.

Successful applicants will be expected to submit a brief report on the conclusion of their visit.

Four copies of all documents should be submitted to

Dr D. A. S. Compston,
Department of Neurology,
University Hospital of Wales,
Heath Park,
Cardiff CF4 4XW, UK

Reduced Subscription Rates

A reduced subscription rate (£20.00 per annum) is available to young subscribers under the age of 40 years, who are in a training post in clinical neurology or in the neurosciences in the UK. Applications for this special rate should be made to Dr D. A. S. Compston, Department of Neurology, University Hospital of Wales, Heath Park, Cardiff CF4 4XW, UK with a letter from the head of department confirming the applicant's eligibility.

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Hereditary sensory neuropathy with neurotrophic keratitis: description of an autosomal recessive disorder with a selective reduction of small myelinated nerve fibres and a discussion of the classification of the hereditary sensory neuropathies. M. Donaghy, R. N. Hakin, J. M. Bamford, A. Garner, G. R. Kirkby, B. A. Noble, M. Tazir-Melboucy, R. H. M. King and P. K. Thomas 563
Impairment of rapid movement in Huntington's disease. H. Hefter, V. Hömberg, H. W. Lange and H.-J. Freund 585
A cognitive neuropsychological case study of anomia: implications for psychological models of word retrieval. J. Kay and A. Ellis 613
Retinal vascular abnormalities in facioscapulohumeral muscular dystrophy: a general association with genetic and therapeutic implications. R. B. Fitzsimons, E. B. Gurwin and A. C. Bird 631
Pathological eye-head coordination in roll: tonic ocular tilt reaction in mesencephalic and medullary lesions. T. Brandt and M. Dieterich 649
Bilateral occlusion of the internal carotid arteries: presenting symptoms in 74 patients and a prospective study of 34 medically treated patients. J. P. H. Wade, W. Wong, H. J. M. Barnett and P. Vandervoort 667
A morphometric study on sural nerves in metachromatic leucodystrophy. A. Bardosi, R. L. Friede, S. Ropte and H. H. Goebel 683
A reassessment of the accuracy of reinnervation by motoneurons following crushing or freezing of the sciatic or lumbar spinal nerves of rats. M. C. Brown and V. J. Hardman 695
Long-latency spinal reflex in man after flexor reflex afferent stimulation. A. Roby-Brami and B. Bussel 707
Neuroendocrine control of vasopressin secretion and its effect on blood pressure in subjects with spinal cord transection. C. J. M. Poole, T. D. M. Williams, S. L. Lightman and H. L. Frankel 727
Neurohypophyseal peptide function during early postoperative diabetes insipidus. J. R. Seckl, D. B. Dunger and S. L. Lightman 737
Recovery from ideomotor apraxia: a study on acute stroke patients. A. Basso, E. Capitani, S. della Sala, M. Laiacona and H. Spinnler 747
Bradyphrenia in Parkinson's disease and psychomotor retardation in depressive illness: an experimental study. D. Rogers, A. J. Lees, E. Smith, M. Trimble and G. M. Stern 761
Natural history of asymptomatic extracranial arterial disease: results of a long-term prospective study. M. Hennerici, H. B. Hülsbömer, H. Hefter, D. Lammerts and W. Rautenberg 777
Facial flushing and sweating mediated by the sympathetic nervous system. P. D. Drummond and W. J. Lance 795
Book reviews 805
Announcements 818

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Brain

A JOURNAL OF NEUROLOGY

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Hereditary sensory neuropathy with neurotrophic keratitis: description of an autosomal recessive disorder with a selective reduction of small myelinated nerve fibres and a discussion of the classification of the hereditary sensory neuropathies. M. Donaghy, R. N. Hakin, J. M. Bamford, A. Garner, G. R. Kirkby, B. A. Noble, M. Tazir-Melboucy, R. H. M. King and P. K. Thomas 563

Impairment of rapid movement in Huntington's disease. H. Hefter, V. Hömberg, H. W. Lange and H.-J. Freund 585

A cognitive neuropsychological case study of anomia: implications for psychological models of word retrieval. J. Kay and A. Ellis 613

Retinal vascular abnormalities in facioscapulohumeral muscular dystrophy: a general association with genetic and therapeutic implications. R. B. Fitzsimons, E. B. Gurwin and A. C. Bird 631

Pathological eye-head coordination in roll: tonic ocular tilt reaction in mesencephalic and medullary lesions. T. Brandt and M. Dieterich 649

Bilateral occlusion of the internal carotid arteries: presenting symptoms in 74 patients and a prospective study of 34 medically treated patients. J. P. H. Wade, W. Wong, H. J. M. Barnett and P. Vandervoort 667

A morphometric study on sural nerves in metachromatic leucodystrophy. A. Bardosi, R. L. Friede, S. Ropte and H. H. Goebel 683

A reassessment of the accuracy of reinnervation by motoneurons following crushing or freezing of the sciatic or lumbar spinal nerves of rats. M. C. Brown and V. J. Hardman 695

Long-latency spinal reflex in man after flexor reflex afferent stimulation. A. Roby-Brami and B. Bussel 707

Neuroendocrine control of vasopressin secretion and its effect on blood pressure in subjects with spinal cord transection. C. J. M. Poole, T. D. M. Williams, S. L. Lightman and H. L. Frankel 727

Neurohypophyseal peptide function during early postoperative diabetes insipidus. J. R. Seckl, D. B. Dunger and S. L. Lightman 737

Recovery from ideomotor apraxia: a study on acute stroke patients. A. Basso, E. Capitani, S. della Sala, M. Laiacona and H. Spinnler 747

Bradyphrenia in Parkinson's disease and psychomotor retardation in depressive illness: an experimental study. D. Rogers, A. J. Lees, E. Smith, M. Trimble and G. M. Stern 761

Natural history of asymptomatic extracranial arterial disease: results of a long-term prospective study. M. Hennerici, H. B. Hülsbömer, H. Hefter, D. Lammerts and W. Rautenberg 777

Facial flushing and sweating mediated by the sympathetic nervous system. P. D. Drummond and W. J. Lance 793

Book reviews 805

Announcements 818

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HEREDITARY SENSORY NEUROPATHY WITH NEUROTROPHIC KERATITIS

DESCRIPTION OF AN AUTOSOMAL RECESSIVE DISORDER WITH A SELECTIVE REDUCTION OF SMALL MYELINATED NERVE FIBRES AND A DISCUSSION OF THE CLASSIFICATION OF THE HEREDITARY SENSORY NEUROPATHIES

by MICHAEL DONAGHY,[1] R. N. HAKIN,[2] J. M. BAMFORD,[2] A. GARNER,[3] G. R. KIRKBY,[4] B. A. NOBLE,[4] M. TAZIR-MELBOUCY,[5] R. H. M. KING[5] *and* P. K. THOMAS[1,5]

(From the [1]Institute of Neurology and the National Hospital for Nervous Disease, Queen Square, London, [2]St. Luke's Hospital, Bradford, West Yorkshire, [3]Department of Pathology, Institute of Ophthalmology, London, [4]Department of Ophthalmology, Leeds General Infirmary, and the [5]Department of Neurological Science, Royal Free Hospital School of Medicine, London)

SUMMARY

A Kashmiri family with 3 members affected by a congenital sensory and autonomic neuropathy and corneal opacification is described. The 3 affected cases were offspring of consanguinous marriages in two generations; autosomal recessive inheritance is therefore probable. Pain and temperature sensation was lost in the limbs with a resulting mutilating acropathy. Sudomotor function was also impaired. Motor function, tendon reflexes, kinaesthetic sensation and sensory nerve action potentials were normal. Sural nerve biopsy showed a selectively reduced small myelinated nerve fibre population. Corneal histology revealed neurotrophic keratitis.

The classification of the hereditary sensory and autonomic neuropathies is discussed. This family represents a previously unrecognized variant.

INTRODUCTION

The early literature contains reports of familial cases in which the salient clinical abnormality was the development of a mutilating acropathy, predominantly affecting the lower limbs. Such cases were frequently ascribed to lumbosacral syringomyelia (Nélaton, 1852; Bruns, 1903; Göbell and Runge, 1917; Schultze, 1917; Weitz, 1924; Riley, 1930; Van Epps and Kerr, 1940). They are difficult to assess in retrospect because of the lack of pathological documentation, but probably represent instances of hereditary sensory neuropathy. The recognition that such cases could be due to a hereditary sensory neuropathy came with the report by Ogryzlo

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(1946) on 4 affected individuals from a sibship of 12 from Newfoundland, the parents being clinically normal. The inheritance was probably autosomal recessive. The onset of symptoms was in early life with distal sensory loss affecting all modalities. Nerve biopsy demonstrated loss of nerve fibres.

The fact that the sensory loss in some cases mainly affected pain and temperature sensibility was the reason why many earlier authors had attributed this to 'lumbosacral syringomyelia'. In these cases, the inheritance was usually autosomal dominant. The first demonstration that they were also due to a sensory neuropathy was provided by Jughenn *et al.* (1949) in a single case that came to autopsy. Loss of myelinated nerve fibres, perineurial thickening and Schwann cell proliferation were observed. Subsequently Denny-Brown (1951), again in a dominantly inherited family previously reported by Hicks (1922) as hereditary perforating ulceration of the feet, considered that the primary defect was a degeneration of dorsal root ganglion cells and introduced the term 'hereditary sensory radicular neuropathy'.

In an attempt to classify hereditary sensory neuropathies in terms of their genetic and clinical features, Dyck and Ohta (1975) later categorized these former cases which showed autosomal recessive inheritance and congenital sensory loss affecting all modalities distally in the limbs as hereditary sensory neuropathy (HSN) type II. Those with autosomal dominant inheritance and an onset of symptoms most frequently during the second and third decades of life and who showed a predominant loss of pain and temperature sensibility were classified as HSN type 1. Nevertheless there is considerable clinical overlap between the two conditions (Asbury and Johnson, 1978).

The term congenital insensitivity to pain was formerly employed to indicate the absence of recognition of pain and a lack of reaction to painful stimuli from birth. In such cases in which there was accompanying anhidrosis, Swanson *et al.* (1965) and Bischoff and Curti (1977) established that there was a selective loss of unmyelinated axons in the peripheral nerves and a deficiency of Lissauer's tract. Similarly, congenital insensitivity to pain in association with familial dysautonomia was shown by Aguayo *et al.* (1971) to be related to a severe deficiency of unmyelinated axons and a lesser depletion of large myelinated axons. Both of these conditions are of autosomal recessive inheritance and were classified by Dyck and Ohta (1975) as HSN IV and III, respectively.

In the present study, a family is described in which a sensory neuropathy, probably congenital and of autosomal recessive inheritance was found to be associated with loss of small myelinated fibres. The family is unique in that the neuropathy was consistently associated with neurotrophic keratitis.

CASE REPORTS

All the family members originated from Kashmir. The 3 members affected by sensory neuropathy and corneal opacification (IV.4, IV.7, V.4) result from two first cousin marriages (fig. 1). Family members III.4, IV.3,6,7,8,10,12,13 were all normal on examination and were unaware of any other affected family members.

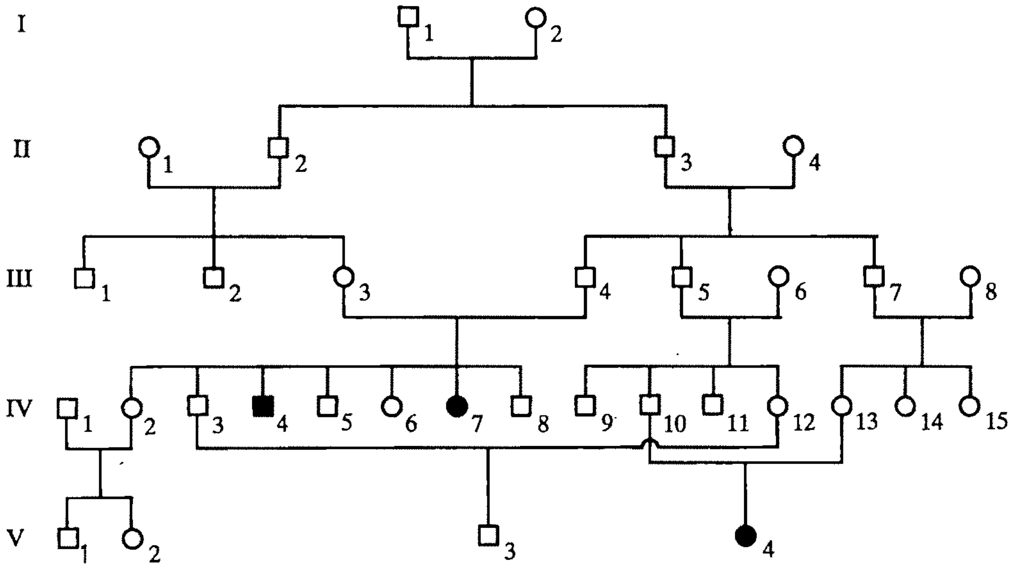


FIG. 1. Pedigree.

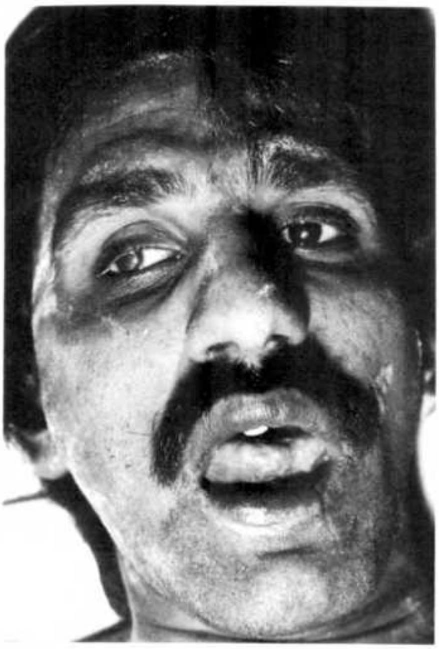
Case IV.4

This 26-yr-old man had a normal birth and did not suffer unexplained fevers during infancy. Bilateral corneal opacification had been noted at about 4 months of age. Ulceration of the tip of the tongue developed at the age of 3 yrs. A sore on the lip became a cleft through which drinking fluids would leak until the defect was closed surgically (fig. 2). From the age of 5 yrs he was aware that he did not feel pain if he cut his hand and that wounds took a long time to heal. He has never been able to feel pain or temperature with his hands or feet. Frequent whitlows have led to loss of terminal finger pulp and deformities of the toes, and autoamputation of one toe. Skin ulcers requiring grafting have affected his feet (fig. 3). He can feel pain and temperature on the trunk and face, has experienced abdominal pain and suffers discomfort if foreign objects lodge in his conjunctivae. Deteriorating vision due to corneal opacities led to a corneal transplant to the right eye at the age of 25 yrs.

Examination revealed mutilating acropathy affecting the feet (fig. 3) and fingers with loss of terminal digital pulp. The tip of the tongue was absent (fig. 2). Mentation, muscle bulk and power, the tendon reflexes, light touch, vibration and joint position sense, and 2-point discrimination were normal. The painful elements of pin-prick sensation, and tickle sensation, were totally absent in the limbs below the elbows and knees, over the tip of the tongue and on the scalp. Mild hyperpathia to pin prick was present on the trunk. Temperature sensation was impaired over the whole body. The corneal reflex was normal on the left but absent from the right-sided corneal graft. Tear secretion was normal.

Ophthalmological examination. Visual acuity was 6/12 in the left eye. The left cornea showed scarring affecting the mid and deeper zones of the stroma with cysts, clefts and pigment spicules within it, and clumping of pigment on the endothelium in the region of the scar (fig. 4). The corneal epithelium was intact and there was no clinical evidence of vascularization of the scar.

Laboratory investigations. The following were normal: routine haematology, plasma urea and electrolytes, blood sugar, serum immunoglobulins and protein electrophoresis, thyroid function, blood lead, vitamin B_{12} and syphilis serology, 24 h urinary vanillyl mandelic acid excretion, audiometry and psychometry.



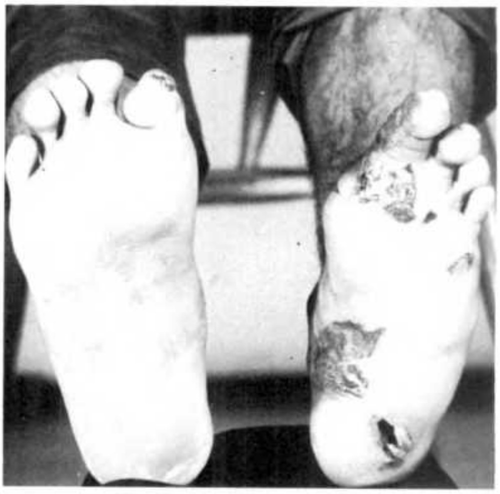


FIG. 2 (*left*). *Case IV.4*, showing traumatic amputation of the tip of the tongue and perioral scars. The right cornea is cloudy, related to chronic rejection of a corneal graft.

FIG. 3 (*right*). *Case IV.4*, showing chronic ulceration of the feet and loss of the left hallux.

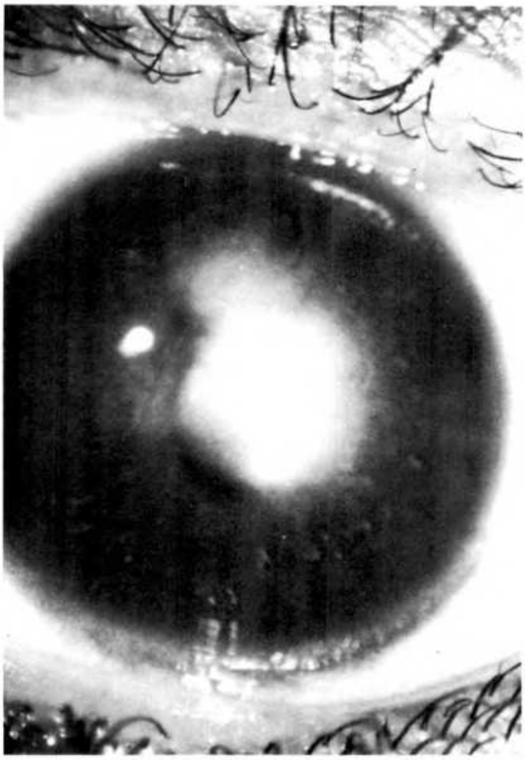


FIG. 4. *Case IV.4*, showing opacification of the central portion of the left cornea.

Neurophysiological investigations. Sensory and motor nerve conduction, and needle electromyography of the first dorsal interosseous muscle of the hand and the tibialis anterior were normal (Table 1), as were somatosensory evoked potentials on stimulation of the posterior tibial nerve at the ankle (N20 lumbar 25 ms, 12 μV; P40 cortex 39 ms, 0.9 μV).

Autonomic function. Sweating was examined on the ventral surface of the body and limbs which were coated with Edicol Pinceau 4R 1G starch BPC and inspected for discolouration after raising the body temperature by 1° C. Sweating was incomplete and occurred only in the areas recorded in fig. 5.

Blood pressure lying was 122/74 mmHg and with 60° tilt was 115/64 mmHg. Sinus arrhythmia was present during deep breathing (55 to 85 beats/min). Carotid massage caused bradycardia.

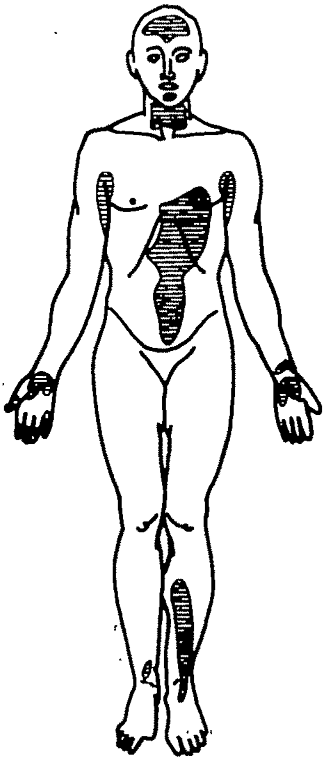


FIG. 5. *Case IV.4.* Sweat test. The shaded areas indicate residual areas of sweating.

TABLE 1. NERVE CONDUCTION STUDIES

	Motor								*Sensory action potentials*			
	Ulnar			*Median*		*Peroneal*			*Ulnar*		*Sural*	
Case	*MCV*	*DL*	*F*	*MCV*	*DL*	*MCV*	*DL*	*F*	*Amp.*	*Latency*	*Amp.*	*Latency*
IV.4	56	3.1	28	—	—	41	7	59	10	3	7	3.7
IV.7	—	—	—	63	3.2	—	—	—	8	2.1	5	3.5

MCV = motor conduction velocity, m·s^{-1}; DL = distal motor latency, ms; F = F wave latency, ms; Amp. = amplitude, μV; Latency = latency to peak, ms.

Case IV.7

This 11-yr girl, sister of Case IV.4, had a normal birth and infancy. Bilateral corneal opacification was noted at 1 yr of age. An ulcer appeared on the tip of the tongue at the age of 3 yrs and even when she subsequently bit off the tip of her tongue she appeared free of pain. At the age of 4½ yrs bilateral keratitis with perforation and adherence of the iris to the cornea on the right was recorded at ophthalmological consultation. By the age of 5 it was clear that she could not appreciate pain or temperature with her hands, feet, anterior tongue or around the nose. Trophic skin ulcers and bony deformity subsequently appeared in the feet. Muscle bulk, power, tendon reflexes and joint position sense were normal. Histamine flare was normal in the areas of reduced pain sensation. There was no postural hypotension and sinus arrhythmia was normal. The cornea and conjunctivae of both eyes were anaesthetic. Tear secretion was normal.

Ophthalmological examination. The visual acuity was no light perception in the right eye and 6/60 in the left. The periphery of the right cornea was clear but its centre bore a dense scar that was superficially vascularized. The iris was adherent to the scarred area. A penetrating keratoplasty had been performed on the left cornea and the specimen was available for histological examination.

Nerve conduction studies. Motor conduction velocity and sensory nerve action potentials were normal (Table 1).

Case V.4

This girl had a normal birth. The eyes were said by the family to have been normal at birth but bilateral corneal opacification was noted at 6 months of age. She may have had a seizure when aged 6 months. When examined at 18 months of age she walked normally, did not speak, and had early trophic changes on the lips and fingertips. A response to pin prick was absent from the hands and normal from the trunk. Both conjunctivae were anaesthetic.

Ophthalmological examination. By 2 yrs of age penetrating keratoplasty for central corneal opacity had been performed on both eyes and one cornea was available for histological examination.

MORPHOLOGICAL INVESTIGATIONS

Nerve Biopsy

Sural nerve fascicular biopsy from a site immediately posterior to the lateral malleolus was obtained under local anaesthetic from Case IV.4 in February, 1985.

Methods. The specimen was fixed for 3 h at 4° C in 3% glutaraldehyde in PIPES buffer (Baur and Stacey, 1977), washed in buffer and postfixed in 2% osmium tetroxide in PIPES buffer. After dehydration through graded concentrations of ethanol, the specimen was embedded in Araldite using 1, 2 epoxypropane as an intermediary. Semithin sections (1 μm) for light microscopy were stained with thionin and acridine orange (Sievers, 1971). Thin sections for electron microscopy (JEOL 100 SX) were stained with 12.5% methanolic uranyl acetate and lead citrate. Myelinated fibre density and size-frequency distributions were obtained using a Kontron Videoplan image analysis system connected to a Leitz Ultraphot. Morphometry of unmyelinated axons was undertaken on electron microscope montages of approximately 10% of the fascicular area at a final magnification of ×8000. Single fibre preparations were obtained by teasing in Araldite, employing the method described by Spencer and Thomas (1970); 136 fibres were isolated.

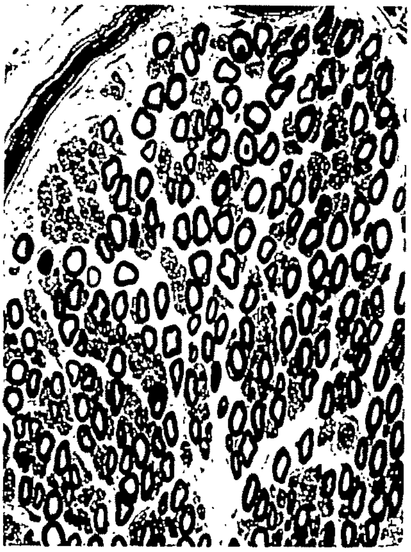


FIG. 6. *Case IV.4.* Transverse section of portion of sural nerve biopsy specimen showing relative lack of small myelinated nerve fibres. Thionin and acridine orange stain, × 530.

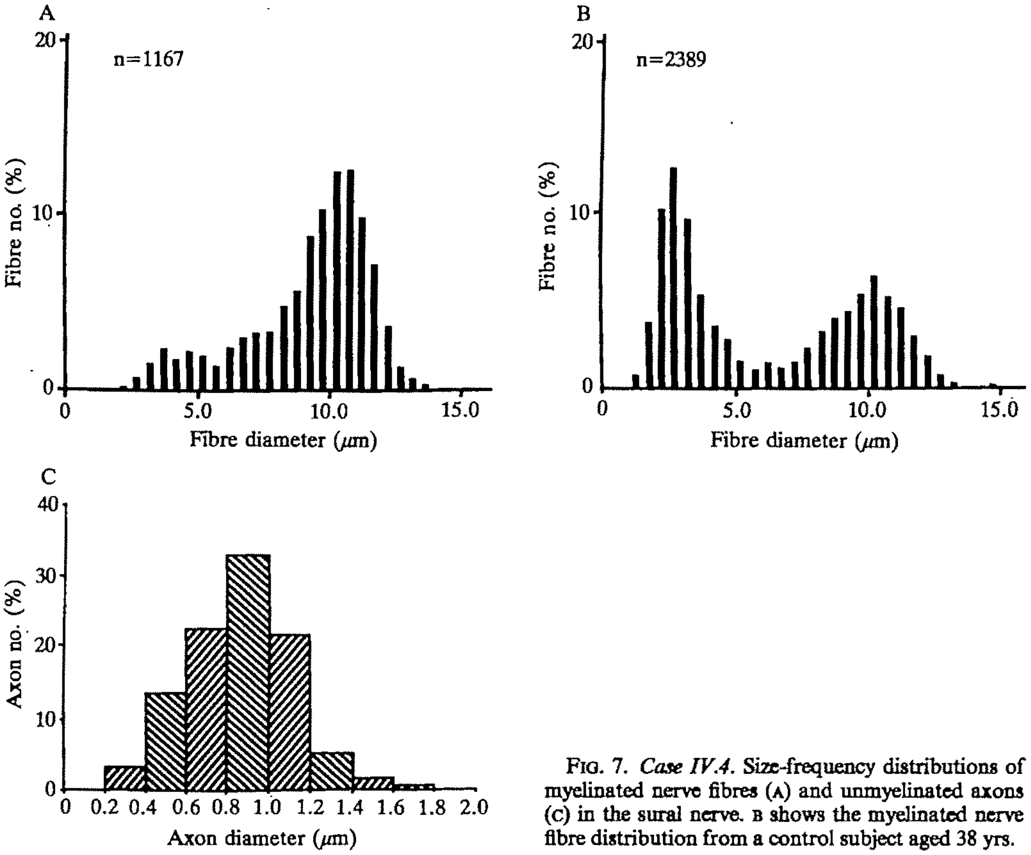


FIG. 7. *Case IV.4.* Size-frequency distributions of myelinated nerve fibres (A) and unmyelinated axons (C) in the sural nerve. B shows the myelinated nerve fibre distribution from a control subject aged 38 yrs.

Results. Transverse sections of the nerve biopsy specimens showed a lack of small myelinated fibres (fig. 6). Myelinated fibre density was reduced at 4726/mm^2 (normal range 7500–10 000/mm^2, Jacobs and Love, 1985). A fibre size-frequency histogram confirmed a striking selective reduction in the smaller diameter myelinated fibre peak (fig. 7A, B). No active fibre degeneration or demyelination was seen in the semithin sections, but occasional regenerative clusters, in slightly excessive numbers for the patient's age, were present. No hypertrophic changes were encountered. The teased fibre preparations showed a normal relationship between internode length and fibre diameter, apart from three fibres with intercalated remyelinated segments and one regenerated fibre with uniformly reduced internode length. This amount of abnormality is within normal limits for the patient's age.

On electron microscopy, the unmyelinated fibres were morphologically normal (fig. 8). The density of unmyelinated axons was increased at 76 000/mm^2 (normal range 30 000–40 000/mm^2, Jacobs and Love, 1985), this presumably being related mainly to the reduction in numbers of small myelinated fibres. As a whole nerve biopsy was not performed, total fascicular area and hence an estimate of the

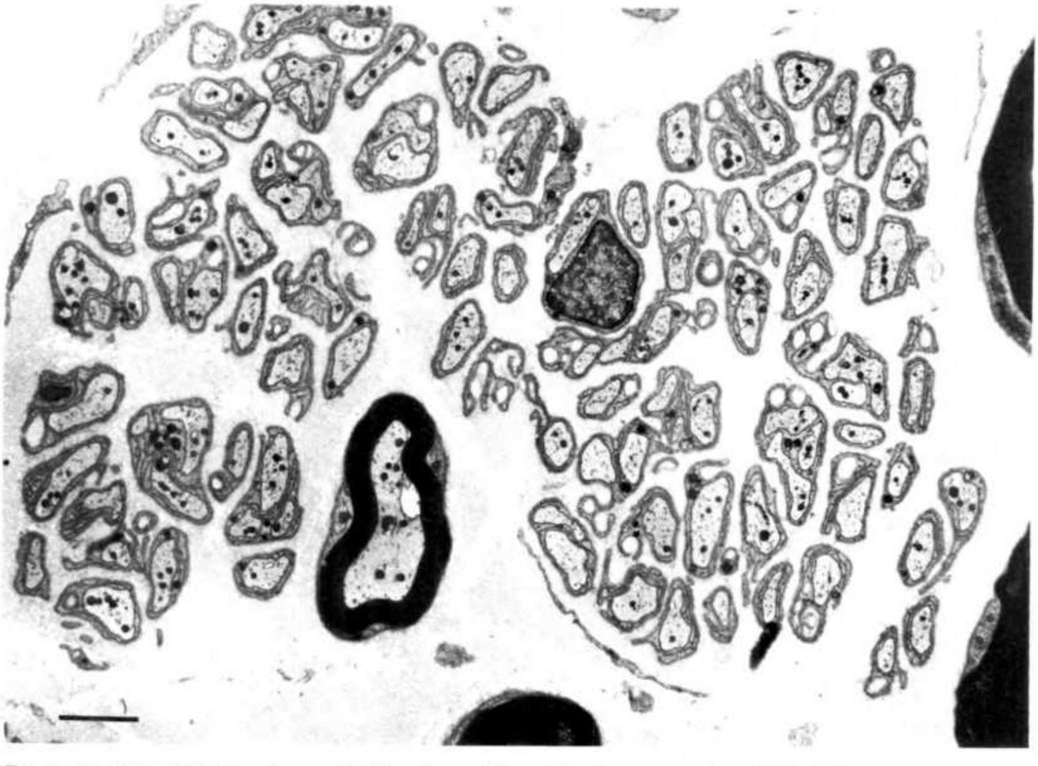


FIG. 8. *Case IV.4*. Electron micrograph of sural nerve biopsy showing group of morphologically normal unmyelinated nerve fibres. Bar = 2 μm.

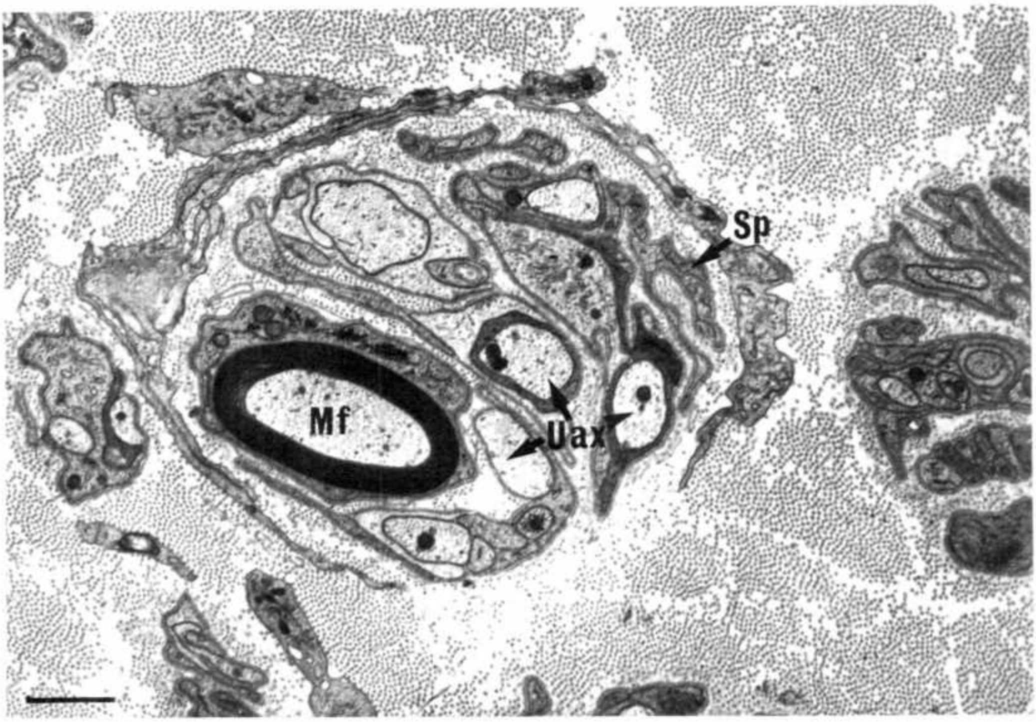


FIG. 9. *Case IV.4.* Electron micrograph of sural nerve biopsy showing regenerative cluster comprised of one myelinated fibre (Mf) and several nonmyelinated axons (Uax) with associated Schwann cell processes (Sp). Bar = 1 μm.

absolute unmyelinated axon count could not be obtained. The size distribution of unmyelinated axons was normal (fig. 7C). The presence of regenerative clusters derived from myelinated fibres was confirmed (fig. 9). There were also occasional stacks of flattened Schwann cell processes of the type that follow the degeneration of Remak fibres (Ochoa, 1978). No giant vacuolated fibroblasts of the type reported by Schoene *et al.* (1970) in hereditary sensory neuropathy were observed.

Corneal Histology

Corneal tissue was available for histological study from Cases IV.7 and V.4, obtained at the time of corneal grafting performed at the ages of 13 yrs and 18 months, respectively. The specimens were fixed in formalin, embedded in paraffin wax and stained with haematoxylin and eosin and the periodic acid-Schiff technique.

IV.7. The epithelium was variable in thickness with atrophy in several places and loss of much, but not all, of Bowman's zone. There was some stromal vascularization and scarring with a very few scattered lymphoctyes. Descemet's membrane and the endothelium were normal.

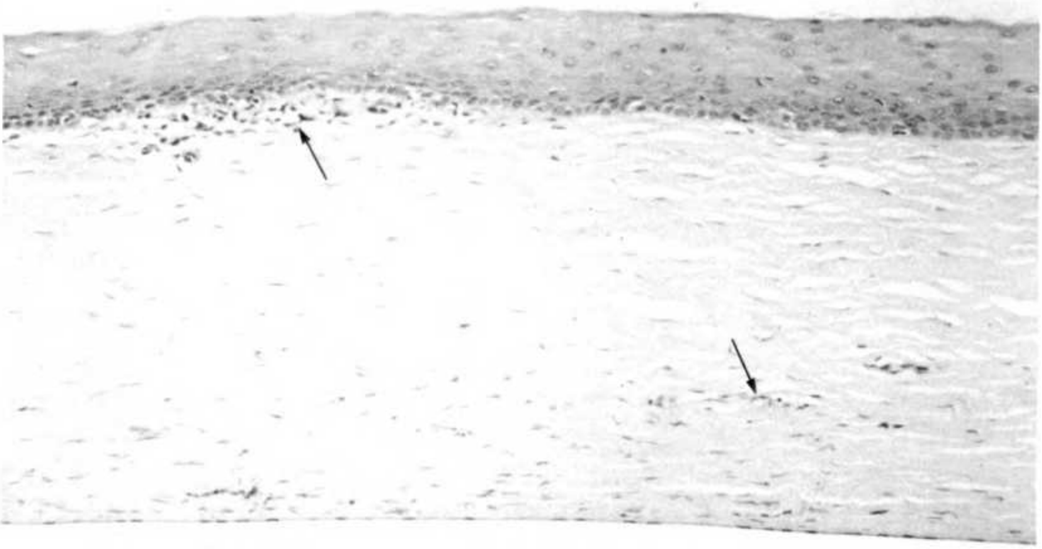


FIG. 10. *Case V.4.* Cross-section of the full thickness of the cornea showing a slightly thickened epithelium in direct contact with the substantia propria, the normal acellular Bowman's zone between these two structures having failed to develop. There is focal hypercellularity of the collagenous stroma associated with some vascularization (arrows). Descemet's membrane is narrow and difficult to identify at this magnification. Haematoxylin and eosin, × 180.

V.4. The corneal epithelium was acanthotic and thickened, but without keratinization, and rested on a basement membrane that was in direct apposition to the lamellar collagen and the substantia propria, there being no identifiable Bowman's zone (fig. 10). A few lymphocytes were present in the stroma, chiefly in the vicinity of infiltrating blood vessels. Descemet's membrane was intact if slightly narrow (fig. 11). Oxytalan fibres were not present (these are an elastic tissue precursor normally found in Descemet's membrane in early childhood which disappear in later life). The endothelium was morphologically normal and of normal density.

DISCUSSION

Hereditary Sensory Neuropathy with Neurotrophic Keratitis

The cases described in this report, from a single family, may represent a unique disorder. All affected individuals exhibited insensitivity to pain, manifested from childhood and possibly congenitally, related to a sensory neuropathy. Clinical examination showed selective loss of pain and temperature sensation which was maximal distally. This had led to a mutilating acropathy and also to facial and tongue injury. Motor function and large fibre sensory modalities were preserved.

The only detectable autonomic manifestation was widespread anhidrosis. This may have contributed to the acropathy by causing dryness and fissuring of the skin.

Sural nerve biopsy revealed selective loss of small myelinated fibres and a normal density of unmyelinated axons. The presence of occasional stacks of flattened Schwann cell processes unassociated with axons suggests that some degeneration of unmyelinated axons may have occurred. No evidence of active myelinated fibre breakdown was encountered, but the finding of occasional regenerative clusters indicates that some degeneration and subsequent regeneration of myelinated fibres had also occurred. These appearances were not frequent but were considered to be excessive for the patient's age. Some continued progression of the neuropathy is therefore implied although, clinically, there was no positive indication of this. The development of increasing mutilating changes may merely represent the consequences of persisting pain and temperature sensory loss.

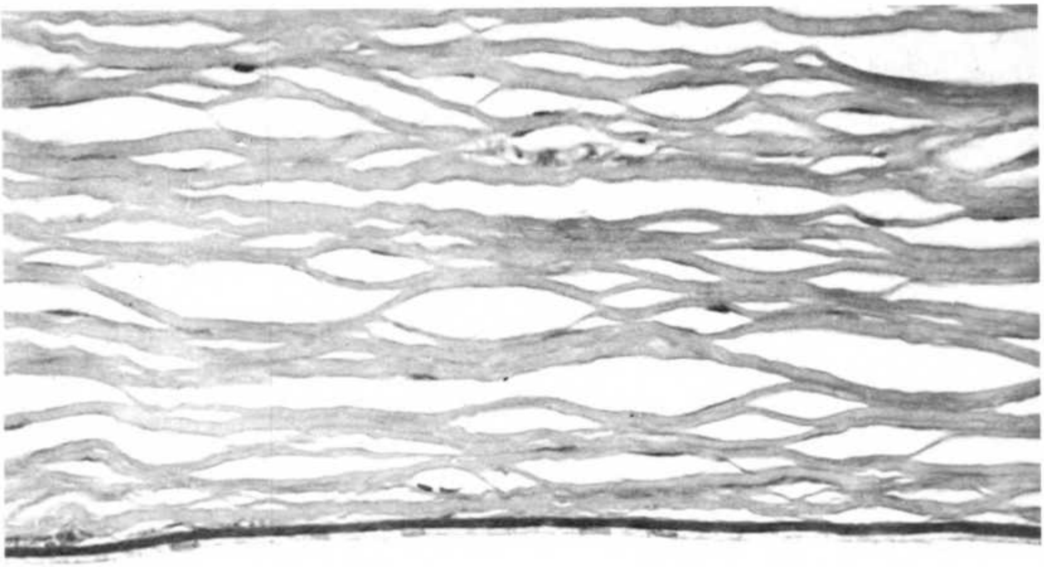


FIG. 11. *Case V.4.* Deep aspect of the cornea showing an even but marginally narrow Descemet's membrane (2.5 μm compared with the 3–4 μm usual at this age). The endothelial lining is continuous and not unduly sparse. Periodic acid-Schiff, × 450.

This pattern of fibre loss, namely a selective reduction in the small myelinated nerve fibre population with preservation of the large myelinated and unmyelinated axons, has been observed previously in 2 cases, both of whom had a congenital sensory neuropathy. The first (Low *et al.*, 1978) was a 6-yr-old girl with recurrent ulceration of her extremities dating back to the age of 7 months, associated with degenerative arthropathy of the ankles. There were no motor abnormalities, the tendon reflexes were preserved and the only detectable sensory loss was for pain and temperature distally in the lower limbs and for pain distally in the upper limbs. Autonomic function was normal, including sweating, apart from anisocoria, and defective pupillary reaction to light on one side. Nerve conduction studies were normal. The second case (Dyck *et al.*, 1983) was a 14-month-old child with selective and universal loss of pain sensation but no other apparent neurological abnormalities except for some evidence of reduced sudomotor function and probable psychomotor retardation. Neither case had a positive family history and there was no definite evidence of consanguinity. It was assumed by Dyck *et al.* (1983) that these 2 cases were likely to have a genetic basis, although it would not be possible to exclude an environmental factor operating in utero in the absence of a family history and evidence of a progressive neuropathy.

The unique features of our family are, first, that this form of sensory impairment with the same pattern of nerve fibre loss on nerve biopsy has been observed as an autosomal recessive trait. The second feature is its association with bilateral corneal opacification, the corneal periphery remaining clear. This corneal opacification was probably not present at birth but developed simultaneously in both eyes of each patient during the first few months or years of life.

A major question is whether the corneal abnormality was merely secondary to the neuropathy or whether it was a separate manifestation of the abnormal gene which caused the neuropathy. Since the relatives recalled that the corneas of Case V.4 were initially clear, a congenital disorder such as sclerocornea or Peter's anomaly has to be discounted. Definite clinical evidence of a traumatic keratitis was only obtained for one of the six corneas, the right eye of Case IV. The nature of the stromal scarring and vascularization, together with the presence of a few scattered leucocytes, is consistent with a postinflammatory disorder. So far as the pathogenesis is concerned, the bilateral simultaneous onset observed in all 3 patients points to an underlying endogenous disturbance, as opposed to a simple infective or traumatic episode. In view of the evidence in other tissues of a sensory nerve defect it is conceivable that the basic pathogenesis of the corneal changes is also neurotrophic, the precise mechanism being obscure but possibly an outcome of vasomotor disturbance at the periphery and associated metabolic consequences (Sigelman and Friedenwald, 1954). Certainly the histological findings compare with those previously described in neurotrophic keratitis (Spencer, 1985).

Of the numerous reported cases with hereditary sensory neuropathy, only one sibship apart from our own has exhibited central corneal opacification. A disorder in Navajo Indian children with the autosomal recessive inheritance of corneal opacity associated with mutilating acropathy, painless long bone fractures, cutaneous ulceration, areflexia, abnormal nerve conduction and severe loss of myelinated fibres in the sural nerve was described by Appenzeller *et al.* (1976). The corneal opacification in these cases was attributed to trauma rather than developmental anomaly. Corneal histology was not reported. Moreover, the pattern of nerve fibre loss resembles that of type II HSN (Ohta *et al.*, 1973) rather that the selective diminution in the small myelinated fibre population seen in our family.

The rarity with which corneal opacification is encountered in hereditary neuropathy suggests that it is not an automatic consequence of the neuropathy. Its invariable association with the neuropathy in our cases and those of Appenzeller *et al.* (1976) raises the possibility that it is a postnatal anomaly of the cornea caused by the abnormal gene responsible for the neuropathy, or by a closely linked gene. The association of the neuropathy and the keratopathy in two generations in our family makes it unlikely that more than one gene is involved.

Classification of the Hereditary Sensory Neuropathies

The classification of the hereditary sensory neuropathies has so far been based on a combination of the clinical and genetic features (Dyck and Ohta, 1975; Thomas, 1975; Asbury and Johnson, 1978). These conditions may be associated with autonomic manifestations which are sometimes the salient aspect of the clinical presentation. Dyck *et al.* (1983) therefore suggested that this group of disorders could appropriately be termed the hereditary sensory and autonomic neuropathies in view of the overlap between these two manifestations. Ultimate characterization will depend upon identification of the abnormal genes and gene products. Until then it is clinically useful to categorize them in terms of their pattern of inheritance in combination with their clinical and pathological features. Autosomal dominant, autosomal recessive and possible X-linked recessive pedigrees have been identified. A tentative classification is given in Table 2. Occasional patients with peroneal muscular atrophy display a severe distal sensory loss leading to a mutilating acropathy (England and Denny-Brown, 1952; Dyck *et al.*, 1965;

TABLE 2. CLASSIFICATION OF HEREDITARY SENSORY AND AUTONOMIC NEUROPATHIES (HSAN)

- Autosomal dominant inheritance
  - Dominantly inherited sensory neuropathy (Denny-Brown, 1951) (HSAN I*)
  - Dominantly inherited sensory neuropathy with paraplegia (Cavanagh *et al.*, 1979)
- Autosomal recessive inheritance
  - Recessively inherited sensory neuropathy (Ohta *et al.*, 1973) (HSAN II*)
  - Hereditary anhidrotic sensory neuropathy (Swanson, 1963) (HSAN IV*)
  - Familial dysautonomia (Riley *et al.*, 1949) (HSAN III*)
  - Hereditary sensory neuropathy with neurotrophic keratitis (present family)
  - Recessively inherited sensory neuropathy with spastic paraplegia (Cavanagh *et al.*, 1979)
- X-linked recessive inheritance
  - X-linked recessive sensory neuropathy (Jestico *et al.*, 1985)
- Uncertain status
  - Hereditary sensory neuropathy with dysautonomia (Nordborg *et al.*, 1981)
  - Congenital sensory neuropathy with selective loss of small myelinated fibres (Low *et al.*, 1978; Dyck *et al.*, 1983) (HSAN V*)

* Classification of Dyck *et al.* (1983)

Ben Hamida *et al.*, 1981). One such family was described by Thomas *et al.* (1974) in whom an earlier diagnosis of 'lumbosacral syringomyelia' was revised to dominantly inherited type I hereditary motor and sensory neuropathy (HMSN). The prominence of the motor signs in such cases makes it more satisfactory for them to be classified as HMSN. Whether families with severe sensory loss are genetically distinct is so far not established. Linkage studies have not yet been reported.

Autosomal dominant forms. The main disorder in this category is the form first adequately described by Denny-Brown (1951). It comprises a distal sensory neuropathy with an onset most commonly in the second or third decades. Sensory loss initially affects mainly pain and temperature appreciation. Dyck *et al.* (1971) and Dyck (1984) found loss of myelinated axons of all diameters and of unmyelinated axons. This was least for large myelinated fibres, intermediate for small myelinated axons and greatest for unmyelinated axons. Spontaneous pain is often a feature. This form has been designated type I hereditary sensory neuropathy by Ohta *et al.* (1973).

Cavanagh *et al.* (1979) reported the occurrence of a sensory neuropathy accompanied by a spastic paraplegia of probable autosomal dominant inheritance. As the salient clinical feature was the sensory neuropathy and the accompanying mutilating acropathy rather than the spastic paraplegia, it is appropriate for this condition to be included amongst the hereditary sensory neuropathies.

Autosomal recessive forms. The most important disorder in this category consists of those cases described as congenital sensory neuropathy (Murray, 1973), progressive sensory neuropathy of childhood (Johnson and Spalding, 1964) or type II hereditary sensory neuropathy (HSN) (Ohta *et al.*, 1973). Recessive inheritance has been suggested by the involvement of more than one individual in a sibship with normal parents and, at times, parental consanguinity. Similar isolated cases are likely to represent the same condition (Linarelli and Prichard, 1970; Barry *et al.*, 1974; Person *et al.*, 1977; Nukada *et al.*, 1982). In some cases the sensory loss is clearly present from birth or early life (e.g., Wadia and Dastur, 1960; Winkelmann *et al.*, 1962; Johnson and Spalding, 1964; Haddow *et al.*, 1970; Linarelli and Prichard, 1970; Murray, 1973; Barry *et al.*, 1974; Person *et al.*, 1977). All sensory modalities are affected. Because of the preservation of motor function and the early age of onset, distal mutilation tends to be particularly severe. Not all have symptoms from infancy. In some cases given this designation (Nukada *et al.*, 1982) or with otherwise similar clinical features (Adams *et al.*, 1973), disease manifestations have not appeared until the third decade. Ataxia rather than the occurrence of cutaneous sensory loss has at times been the initial feature (Nukada *et al.*, 1982). Minor autonomic involvement occurs, including impotence and disturbances of bladder function (Murray, 1973; Nukada *et al.*, 1982). Nerve biopsies show severe loss of myelinated nerve fibres of all sizes and some reduction in the number of unmyelinated axons (Ohta *et al.*, 1973; Nukada *et al.*, 1982).

The question of progression in recessively inherited sensory neuropathy has given rise to discussion. Murray (1973) considered that in his cases, the congenital neurological disorder was static, the advance in the mutilations that they showed merely being the result of persisting sensory loss. Other patients undoubtedly show progression of neurological signs; moreover, increasing severity of fibre loss of consecutive biopsies has been demonstrated (Nukada *et al.*, 1982). Tamari *et al.* (1980) have suggested that two forms exist: (1) a congenital nonprogressive form, including the cases of Haddow *et al.* (1970) and Murray (1973); (2) a progressive form with an onset later in childhood, including the cases in the 3 families that they described and those of Johnson and Spalding (1964), Schoene *et al.* (1970), Ohta *et al.* (1973) and Jędrzejowska and Milczarek (1976). Not all published cases fall easily into one or other of these subdivisions. Nevertheless, in general, the available evidence makes this possibility worthy of further consideration.

The second clearly identifiable autosomal recessive form is sensory neuropathy with anhidrosis (Swanson, 1963; Brown and Podosin, 1966; Pinsky and DiGeorge, 1966; Vassella *et al.*, 1968) or type IV HSN (Dyck and Ohta, 1975). Affected individuals show congenital insensitivity to pain, loss of sweating and mild mental retardation. There is a virtual absence of unmyelinated axons in the peripheral sensory nerves (Bischoff and Curti, 1977; Goebel *et al.*, 1980), absence of small neurons in the primary sensory ganglia and a reduction in the size of Lissauer's tract (Swanson *et al.*, 1965).

A third distinct condition is the Riley-Day syndrome (familial dysautonomia, Riley *et al.*, 1949). Although autonomic manifestations are the predominant feature, individuals affected with this autosomal recessive disorder also display congenital insensitivity to pain. Aguayo *et al.* (1971), from a nerve biopsy study, demonstrated that there is a severe reduction in the number of unmyelinated axons and a lack of myelinated fibres of largest diameter. There are also reduced numbers of neurons in sympathetic, dorsal root and trigeminal ganglia (Pearson *et al.*, 1971). Nordborg *et al.* (1981) described 3 sporadic cases of a nonprogressive congenital sensory neuropathy and dysautonomia with clinical features that differed in a number of respects from the Riley-Day syndrome. Nerve biopsy showed an almost total loss of myelinated axons and a reduction in the number of unmyelinated axons, this pattern more closely resembling that of type II HSN. It was considered that they probably represented a separate entity, distinct from the Riley-Day syndrome.

Finally, Cavanagh *et al.* (1979) described a sensory neuropathy associated with spastic paraplegia of probable autosomal recessive inheritance, the manifestations being more severe than in the autosomal dominant disorder that they also reported. A further family of this type has recently been identified (G. D. Schott and P. K. Thomas, unpublished).

X-linked recessive sensory neuropathy. There has been a single report of a sensory neuropathy with symptoms that developed during the second decade with possible X-linked recessive inheritance (Jestico *et al.*, 1985). The clinical manifestations resembled those of dominantly inherited sensory neuropathy. Nerve biopsy revealed a generalized loss of myelinated fibres, but particularly those of smaller diameter. Unmyelinated axons were present in normal numbers.

Pathological Basis for Hereditary Sensory Neuropathy

In dominantly inherited sensory neuropathy a progressive loss of dorsal root ganglion cells is assumed to occur (Denny-Brown, 1951). Whether there is a preceding distal axonal degeneration ('dying-back' neuropathy) is not established but this was suggested by the observations of Dyck *et al.* (1971) and Dyck (1984). The 'hyperplastic myelinopathy' affecting myelinated nerve fibres of medium or large calibre found in nerve biopsies from patients in a family with autosomal dominant insensitivity to pain (Comings and Amromin, 1974) represents artefactual myelin damage.

In recessively inherited sensory neuropathy, as already discussed, there is possible clinical evidence for genetic heterogeneity with both a congenital nonprogressive form, and a progressive form, usually with a later onset in childhood (Tamari *et al.*, 1980). Nukada *et al.* (1982) have provided nerve biopsy evidence of continued fibre loss in the latter form.

The sensory neuropathy in the Riley-Day syndrome is probably nonprogressive. In this condition Aguayo *et al.* (1971) postulated a selective developmental arrest for both unmyelinated and large myelinated axons. This they related to interference with the second neuronal migration from the neural crest which gives rise both to small and large neurons. No evidence of degeneration of fibres in the nerve biopsy from their case was detected and thus a developmental failure was assumed.

A further possibility to be considered has been raised by Chimelli and Scaravilli (1986) in the rat mutant 'mutilated foot' (*mf*), which consists of a congenital sensory neuropathy. Here it has been shown that the pathological basis consists of a massive degeneration of dorsal root ganglion cells in the later fetal period which continues for a short time postnatally. It resembles, in excessive form, the 'programmed cell death' that occurs as a normal feature during development. Observations at the appropriate stage are so far not available in congenital sensory neuropathy in man to establish whether this could be the basis. In Case 1 of the series reported by Dyck *et al.* (1983), nerve biopsy at the age of 26 months showed no evidence of acute fibre breakdown, but it was not stated whether there was an excess of denervated Schwann cells to suggest previous fibre degeneration.

In Case IV.4 from the present study, the nerve biopsy appearances indicated a possible mild degree of continuing nerve fibre degeneration and regeneration. Surprisingly few denervated Schwann cells were present in relation to the magnitude of the depletion of small myelinated axons. However, if the fibre loss had occurred at an early age, the denervated Schwann cells may have disappeared (Weinberg and Spencer, 1978). The overall pattern suggests either a failure of development (aplasia) of the neurons giving rise to small myelinated axons, or a predominantly prenatal neuronal degeneration.

Congenital Indifference to Pain

Earlier descriptions refer to cases with congenital indifference to pain (Arbuse *et al.*, 1949; Boyd and Nie, 1949; Westlake, 1952; Critchley, 1956; Fanconi and Ferrazzini, 1957; Silverman and Gilden, 1959), congenital universal insensitivity to pain (Ford and Wilkins, 1938; McMurray, 1950; Baxter and Olszewski, 1960), congenital pure analgesia (Dearborn, 1932) and asymbolia for pain (Schilder and Stengel, 1931). Such patients were stated to be able to distinguish sharp from blunt but not to recognize noxious stimuli as painful anywhere in their bodies, did not exhibit the usual physiological reactions to pain and retained their tendon reflexes (Ogden *et al.*, 1959; Winkelmann *et al.*, 1962). An agnosia for pain was postulated (Jewsbury, 1951).

Occasional cases were the product of consanguinous marriages (Durand and Belotti, 1957; Fanconi and Ferrazzini, 1957) or affected several siblings with normal parents (Thrush, 1973). Autosomal recessive inheritance might thus be suspected. Pathological changes were not recognized in the peripheral nerves, spinal cord or brain (Moffie, 1951; Feindel, 1953; Ogden *et al.*, 1959; Baxter and Olszewski, 1960). These reports are now difficult to analyse and it is not clear whether indifference or asymbolia for pain remains an acceptable entity. No cases have been described in recent years which, after adequate study of the peripheral nerves, have proved not to have a sensory neuropathy. In the family reported by Thrush (1973), the site of the disturbance was considered to be in the CNS. The PNS was believed to be 'relatively intact'. Nerve biopsy was reported as showing some loss of large myelinated fibres with regenerative activity, but morphometry was not undertaken. Retention of the tendon reflexes, as in our cases, is typical of a 'small fibre' neuropathy; it does not exclude peripheral nerve disorder. Likewise, sensory nerve action potentials, which reflect conduction in large myelinated nerve fibres, may be preserved. Dyck *et al.* (1983) pointed out that their Case 1 and that of Low *et al.* (1978) would have been accepted as having normal peripheral nerve histology without morphometric study. The same is true of the present Case IV.4.

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IMPAIRMENT OF RAPID MOVEMENT IN HUNTINGTON'S DISEASE

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SUMMARY

Patients with Huntington's disease (HD) and relatives at risk were examined with respect to their capacity to produce rapid voluntary motor activity. For this purpose, the fastest possible self-paced single isometric forefinger extensions and the fastest alternating forefinger movements were tested. In addition to these fastest voluntary performances, the time course of spontaneous hyperkinetic finger movements and the peak frequency of finger and hand tremor were analysed as a measure of the temporal characteristics of involuntary movements. Comparison of these parameters in HD patients and individuals at risk with age and sex-matched normal controls revealed a significant slowing of all types of contractions or movements in the majority (up to 95%) of the patients and in up to 40% of the relatives at risk. Reaction times were only slightly prolonged, and the abnormalities of the movement parameters showed no correlation with detailed psychometric data. Hence it is unlikely that the disturbance in the execution of rapid motor acts is due to dementia. Tremor was also slower than normal and the hyperkinesias were still slower than the fastest voluntary contractions. It appears from this study that slowness of motor performance is not only evident in Parkinson's disease but may represent a more general dysfunction in basal ganglia disease.

INTRODUCTION

Huntington's (HD) and Parkinson's disease (PD) result from selective involvement of different subpopulations of striatal neurons: the dopaminergic nigrostriatal system in PD and the cholinergic intrinsic and gabaergic output neurons in HD. In spite of the affection of such closely linked circuitries the two disorders are characterized by opposite clinical features: one is hyperkinetic and the other hypokinetic. Despite these different clinical hallmarks the two basal ganglia disorders also have common aspects. Reports describing rigidity and akinesia in rare Westphal variants of HD with early juvenile onset (Westphal, 1883) or in the late stages of the disease (Bonhoeffer, 1936; Denny-Brown, 1960; Campbell *et al.*, 1961) reveal that the clinical features typically seen in PD may sometimes also occur in HD. Besides these rare variants, Hamilton (1908), in examining 27 cases with HD, emphasized the slowness of voluntary movements, the presence of plastic rigidity

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and a flexed posture resembling PD in many of his patients. Herz (1931), in his pioneering monograph in which he introduced frame-by-frame cinematographic analysis for the description of involuntary movements, described clear abnormalities of voluntary motor activity in his patients with HD. He emphasized especially the difficulty of movement initiation, the slowness and irregularity of movement execution and the disharmonic coordination of different body parts resembling 'asynergy'. Bittenbender and Quadfasel (1962) in their review of the literature stated that 'the frequency of occurrence of the rigid form of HD is greater than generally appreciated'.

Various aspects of disturbed motor activity in HD have been revealed by neurophysiological studies. Analysis of eye movements (André-Thomas *et al.*, 1945; Starr, 1967; Avanzini *et al.*, 1979; Oepen *et al.*, 1981; Leopold *et al.*, 1982; Leigh *et al.*, 1983) demonstrated slowness of saccades and a disturbance of smooth pursuit caused by inappropriate intrusion of saccades. Other studies in patients with HD have shown abolition of long-latency stretch reflexes (Noth *et al.*, 1983, 1985), alteration of physiological tremor (Myers and Falek, 1979) and an impairment of postural stability (Valade *et al.*, 1984). Only a few studies have considered voluntary motor control in HD. Petajan *et al.* (1979) described impairment of voluntary control of individual motor units and Starr (1967) presented one example of impairment of fast voluntary limb movements in HD in a paper otherwise concentrating on oculomotor disturbances. Recently Koller and Trimble (1985) described alterations of gait pattern in HD.

Quantitative analysis has so far not clarified whether slowing of movement is a consistent phenomenon in HD or a rare abnormality that appears only in a few variants. This may be due to difficulties in quantifying voluntary movements. We therefore selected out of the wide range of possible movements simple motor tasks which are limited by the properties of the system itself or follow invariant principles. We have analysed two types of rapid voluntary motor performances: the fastest possible single isometric contractions and the fastest alternating movements. For comparison, two forms of rapid involuntary movements, the hyperkinesias and tremor, were also measured. All recordings were made from the index finger of the dominant hand in patients with HD, in their offspring at risk of developing the disease later in life and in an age and sex-matched control group.

METHODS

Patients

A total of 22 patients with a definite diagnosis of HD were examined. Severity of the disorder in these patients was scored according to a modified version (Lange *et al.*, 1983) of the Shoulson-Fahn Score (Shoulson and Fahn, 1979) referred to as DIS. Table 1 gives detailed clinical data of the Huntington's disease (HD) patients in the study: age, sex, duration of choreic symptoms (DUR), severity of choreic symptoms (CHOR), disability score (DIS) and drugs. More than half of the patients (13/22) did not take any drugs, 4 were taking only substituted benzamides such as sulperide or tiapride with dopamine receptor blocking properties but not causing extrapyramidal symptoms; 2 had a

TABLE 1: CLINICAL DATA AND FORMS OF PHARMACOLOGICAL TREATMENT IN THE GROUP OF PATIENTS WITH HUNTINGTON'S DISEASE

	Case	*Age (yrs)*	*Sex*	*DUR*	*CHOR*	*DIS*	*Drugs*
1	(B.B.)	34	M	13	2.5	1.2	TI, BZ, PH
2	(R.H.)	33	F	7	2.5	0.9	TI
3	(P.R.)	39	F	9	1.5	1.6	TI, BZ
4	(S.P.)	45	M	3	2.0	1.7	BU, PH
5	(O.F.)	61	M	10	1.0	0.9	0
6	(S.M.)	53	M	5	1.5	1.7	0
7	(D.R.)	30	M	5	1.5	0.3	IN
8	(H.H.)	42	M	2	1.5	1.3	0
9	(M.I.)	51	F	7	2.5	1.4	0
10	(I.I.)	47	F	3	1.0	0.9	0
11	(T.D.)	41	F	5	1.0	1.3	TI, BZ
12	(W.B.)	47	F	8	2.0	1.8	0
13	(L.K.)	50	F	7	2.5	2.0	TI
14	(B.D.)	43	M	5	1.5	0.5	0
15	(L.W.)	36	M	2	1.0	0.0	0
16	(H.R.)	41	F	4	1.5	0.3	0
17	(R.L.)	52	F	4	2.0	1.2	TI
18	(B.U.)	43	F	12	1.0	1.2	0
19	(T.E.)	28	F	2	1.5	1.2	0
20	(Z.R.)	37	F	3	1.0	0.4	0
21	(M.M)	34	F	3	1.0	0.0	0
22	(K.E.)	62	F	4	1.0	2.3	SU, BA

DUR = duration of choreic movements (yrs). CHOR = severity of chorea during clinical investigation ranging from 0 to 3 (Lange *et al.*, 1983). DIS = disability score (Shoulson and Fahn 1979; Lange *et al.*, 1983; Lange *et al.*, 1984). BU = butyrophenones. SU = sulpiride. PH = phenothiazines. IN = isoniazid. TI = tiapride. BZ = benzodiazepines. BA = baclofen.

combination of tiapride and benzodiazepines and only 2 patients were taking major neuroleptics known to cause parkinsonian features. One patient was on isoniazid alone. None of the patients presented clinically with a significant increase of muscle tone; instead, the majority showed hypotonia.

Forty subjects at risk were examined, all of whom were first generation offspring of patients with definite HD. Standard neurological examination in these individuals was always normal except for the presence of indefinite ('soft') clinical signs (similar to those defined by Young *et al.*, 1986; e.g., slowing of fast hand pronation and supination or finger flexion-extension movements) in 9 at risk subjects. None of them had any evidence of choreiform movements when entering the study. This was assessed by a careful search for the presence of involuntary movements with the at risk patients being asked to remain as still as possible while carrying out distraction tasks such as repetitive subtraction of 7 from 100 or reciting the names of the months backwards. In the 9 subjects at risk for HD with indefinite signs this search revealed some increase in restlessness above the normal values but no hyperkinesia. None of the at risk subjects was taking any drug which might interfere with motor activity except for 1 patient with a high alcohol intake. All at risk subjects with 'soft' signs are marked by special symbols in the figures. We also studied 1 patient with the juvenile rigid 'Westphal' variant of HD and 1 patient with Sydenham's chorea. Clinical data of these patients will be given in the Results section.

A group of 26 normal volunteers recruited from the hospital staff and from outpatients at our institution with vascular headaches, compressive radiculopathy of the lower limbs or minor nonneurological disease served as controls. Controls were matched by age and sex with the patients and the at risk group: each patient was matched for age and sex by a single control subject but the same control subject could match multiple at risk subjects.

Experimental Procedures and Data Analysis

Analysis of tremor. A light-weight Philips type (PR 9366 E/20) accelerometer was taped to the distal phalanx of the index finger of the dominant hand. Patients were seated in a reclining chair and asked to keep their hands outstretched at 90 deg anteversion of the shoulder with the elbow kept straight, the hand pronated and the fingers stretched out horizontally. The ongoing tremor recorded by the accelerometer for a period of 25 s was fed into a Nicolet (Med-80) computer and sampled at a frequency of 80 Hz. The resulting signal was stored on magnetic discs for off-line data analysis. The total period was subdivided into 8 segments and for each of these segments a power spectral density function was computed. The 8 resulting spectra were averaged. From this average spectrum the peak frequency was determined. Series of partially overlapping power spectra were plotted to visualize the time course of variation of peak frequency (for further details regarding filtering, *see* Hömberg *et al.*, 1987).

Analysis of fastest alternating movements. For analysis of fastest alternating index finger movements the accelerometer remained at the distal phalanx of the index finger as described in the preceding section. Subjects were instructed to keep the forefinger outstretched with the wrist stabilized by the contralateral hand, the forearm semipronated and the elbow flexed at 90 deg. In one or two warm-up trials they were trained by the experimenters to perform fastest possible flexion-extension movements at the metacarpophalangeal joint with the index finger kept outstretched. Between the warm-up trials, pauses of at least 2 min were provided to avoid muscular fatigue. The resulting accelerometer signal was digitized as described above at a sampling frequency of 60 Hz. A total recording period of 34 s was subdivided into 16 segments. For each segment the power spectrum density-function was calculated and its peak frequency determined. The maximum of these 16 frequencies was defined as the frequency of maximal voluntary alternating movements. In addition consecutive partly overlapping segments of 4.2 s duration were plotted in the form of hidden line plots to visualize dynamic changes of alternating frequencies.

Fastest isometric voluntary index finger extensions. Subjects and patients were seated in the reclining chair as before. The forearm was fixed in full pronation on a flat support. The index finger was attached to the axis of a bidirectionally sensitive Schaewitz type FTD force transducer by means of a concentric ring adjustable in diameter to individual finger size at the proximal interphalangeal joint. To avoid movements around the wrist, leather straps were attached across the middorsum of the hand, just proximal to the wrist joint and at positions 15 and 30 cm more proximally in the forearm. Bipolar surface EMG electrodes were fixed over the extensor indicis and the flexor digitorum superficialis muscles. Optimal location of electrodes was achieved by obtaining a maximal signal amplitude in both flexion and extension at a given constant force and by ensuring that slowly alternating flexion-extension of the metacarpophalangeal joint resulted in reciprocal activity in agonist and antagonist.

Subjects were instructed to press their index finger against the force transducer as quickly as possible after the occurrence of a 1000 Hz tone of 50 ms duration. The amplitudes of the contractions performed in this simple reaction time paradigm could be chosen deliberately by the subjects, but it was emphasized that the amplitudes were varied from trial to trial, so that a broad distribution of amplitudes was produced. The force signal and the rectified demodulated surface EMG were sampled at a rate of 1 kHz for trial epochs of 1.024 s duration starting 50 ms before stimulus onset, and stored on a magnetic disc; 20 to 30 trials were recorded in every subject.

From the force records the following parameters were extracted by means of an interactive cursor display: (1) reaction time (RT), i.e., the time between tone onset and start of the contraction; (2) contraction time (CT), i.e., the time between start and peak point of the contraction; and (3) contraction amplitude (AM). The remainder of the data analysis will be explained in the Results section.

Recordings of involuntary isometric contractions. In some HD patients the hyperkinetic movements of the fingers occurred with such large amplitudes that they could be compared with voluntary single contractions. For this purpose the patients remained coupled to the force transducer in the same way as described above for the isometric recordings and were told not to move voluntarily and to relax completely. Hyperkinetic fluctuations in isometric force were recorded continuously for periods of several minutes. Since the force transducer used was bidirectionally sensitive, both flexion and extension forces of the hyperkinesic movements could be recorded. From the data stored on discs these involuntary force changes were analysed off-line in the same way as described for rapid isometric contractions in the preceding section.

Other EMG recordings. In some HD patients, the EMG activity during fastest isotonic elbow extension movements and during alternating wrist flexion-extension movements of the dominant arm were studied. Surface EMG electrodes were attached over biceps and triceps brachii or flexor carpi ulnaris and extensor carpi radialis muscles, respectively. The patients were instructed to perform the fastest possible elbow extensions after a tone cue (1000 Hz, 50 ms duration, 70 dB SPL) starting from a resting position of 90 deg flexion of the elbow with the forearm fully supinated and the shoulder elevated to 90 deg. Onset of movement was detected by an accelerometer taped to the forearm. For alternating wrist movements the wrist was held in semipronation, the elbow in 90 deg flexed and the forearm resting on a flat support. Patients were told to move their wrist at a frequency of about 2 Hz as regularly as possible.

In 1 HD patient at a very early stage of disease in whom hyperkinesia was still restricted to the toes on the right, the EMG pattern of these hyperkinetic movements was recorded; surface electrodes were fixed over extensor digitorum brevis and flexor digitorum brevis. An accelerometer was taped to the distal dorsal phalanx of the big toe to detect onset of movements. During the recording, the patient was asked to relax completely with both legs resting on a bench.

Psychometry. For all of the HD patients and at risk subjects in this study, detailed psychometric data were obtained within a period of two weeks around the motor studies. The various psychometric procedures have been described in more detail before (Lange *et al.*, 1983; Hömberg *et al.*, 1986). Briefly the following psychometric tests were performed:

1. The WIP score (Dahl, 1972). This is a short condensed intelligence score encompassing the 'information', 'similarities', 'picture completion' and 'block design' subtests of the German version of the WAIS.
2. The German version of the Raven standard progressive matrices (Raven, 1938; Kratzmeier and Horn, 1980). This test was used to assess reasoning and concept formation independent from language-related abilities and time pressure. In essence this test requires that incomplete visually-presented patterns be completed by selection of 1 of 6 or 8 stimuli. The tasks are ordered in increasing difficulty, with 60 trials presented in 5 blocks of 12 items.
3. The multiple choice-vocabulary test (MWT-B, Lehrl, 1977). This has been shown to be a reliable indicator of the premorbid level of verbal intelligence (Merz *et al.*, 1975). The test requires selection of 1 proper word out of groups of 5 words which always contain 4 nonsense words; 37 of these word groups rank ordered in increasing difficulty are used.
4. The Syndrom-Kurz Test (SKT) (Erzigkeit, 1977). This is a sensitive indicator of impairment of memory, attention and concentration of patients with cognitive impairment. It consists of naming, reproduction of visually-presented material after various time intervals freely or out of a second list of items, ordering of numbers, counting of symbol categories and an interference task where all instances of the letter A have to be read aloud as B and vice versa. This measures 'disposition rigidity' and vulnerability to distraction. All subtests imply time pressure.

Statistical analysis. For group comparisons conventional Student's t tests for uncorrelated means were applied after testing for homogeneity of variances using the F-max test. The relationships between various motor parameters age, psychometry or disability scores were assessed using linear regression analysis and Pearson product-moment correlation coefficients. The normal range for age-dependent movement parameters was defined by 2 SD above and below the age-related regression line for each parameter in the normal population. Covariation ellipses were calculated from the Ciba Geigy Wissenschaftliche Tabellen (Statistik), pp. 219–221.

RESULTS

Most Rapid Single Isometric Index Finger Contractions

Contraction times. The fastest voluntary single index finger extensions are prolonged in patients with HD, as can be seen even in single trials. Fig. 1 shows a single trial of the reaction time paradigm for fastest possible voluntary isometric index finger extensions in a normal subject and an HD patient. In the normal subject a smooth contraction curve results (fig. 1, second row, left side). The extensor (fig. 1, third row) and the flexor EMG (fig. 1, bottom row) both show a single burst with the flexor already being coactivated about 20 to 30 ms after the extensor. This coactivation is typical for rapid isometric contractions (Freund and Büdingen, 1978; Sanes and Jennings, 1984). In the HD patient (fig. 1, right side) the contraction curves show a marked prolongation before peak force is reached. This is caused by a slowing of the corresponding build up of EMG activity. The coactivation pattern of agonist and antagonist is, however, maintained. Similarly the normal 'triphasic' pattern (Wachholder and Altenburger, 1926; Hallett *et al.*, 1975) for fastest isotonic

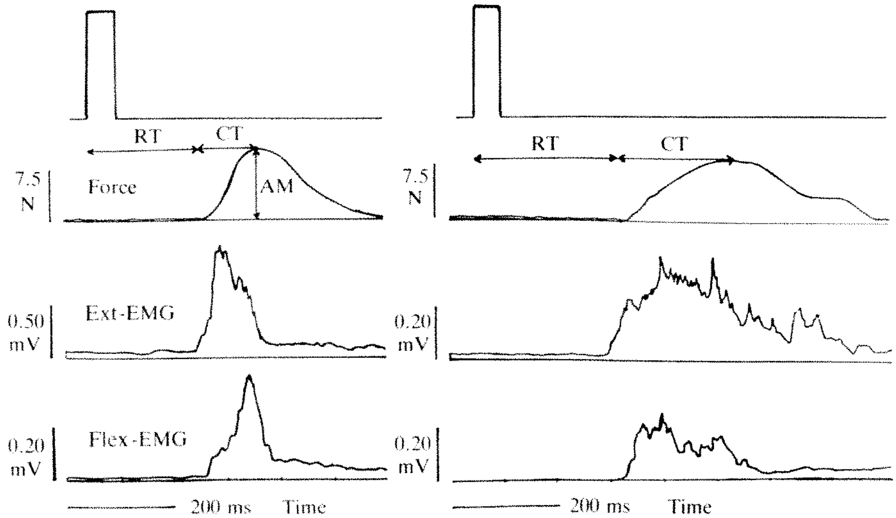


FIG. 1. A single most rapid index finger extension in a normal subject (*left side*) and in a patient with HD (*right side*). In the normal subject the contraction starts 120–170 ms (= reaction time, RT) after the tone signal and reaches peak amplitude in about 100 ms (contraction time, CT). The EMG shows cocontraction of agonist (EXT) and antagonist (FLEX) muscles. In the HD patient RT, CT and the EMG burst duration are prolonged. The normal coactivation pattern is maintained. AM = amplitude.

elbow extensions and the normal reciprocal pattern for alternating wrist movements are maintained. It therefore appears that the proper selection of muscle groups for these simple types of contractions and movements is not impaired in HD.

The calculations of mean contraction times for the different populations would be the next step of data processing. This is, however, not possible at this stage because, as will be shown, contraction time varies with contraction amplitude in many HD patients. Since the task was to perform the contractions as fast as possible at freely selectable amplitudes, for the comparison of contraction times the variation of contraction amplitudes has to be taken into account. It is therefore necessary to establish the contraction time-amplitude relationship first.

Relationship between contraction time and amplitude. In fig. 2 several most rapid contractions of a normal subject (left side) aligned for contraction onset are compared with the most rapid contractions plotted in the same way for 2 typical HD patients representing various stages of the disorder: the example in the middle is from Case 20 (37 yrs; F; CHOR = 1.0; DUR = 3; DIS = 0.4) whereas the example on the right is from the more affected Case 17 (52 yrs; F; CHOR = 2, DUR = 4; DIS = 1.2). In the early stages of HD, contractions are already prolonged. In the normal subject contraction times remain approximately constant irrespective of amplitudes (Freund and Büdingen, 1978). In milder affected cases with HD the variation of the rate of rise of tension may be well preserved and hence contraction time remains independent of amplitude. With further progression of the disease, however, the ability to increase the rate of rise of tension is reduced so that a clear increase of contraction time with amplitude results (fig. 2, right side).

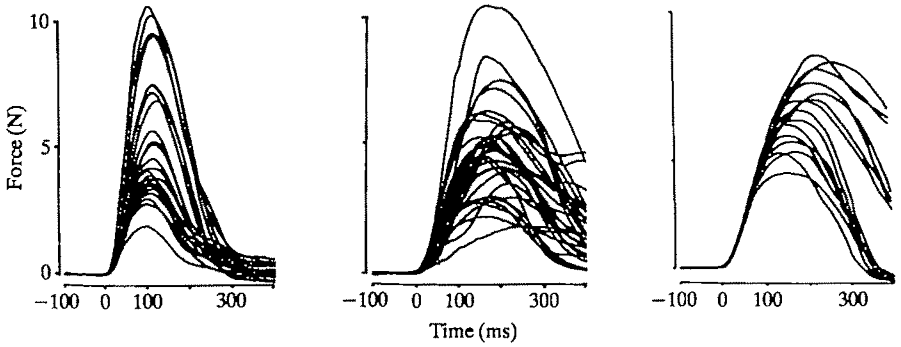


FIG. 2. Amplitude-contraction time relationship in a normal subject (*left panel*) and 2 patients with HD (*right panel*). In the normal (*left panel*) contraction times only slightly increase with larger amplitudes. Two different abnormalities occur in HD patients: contraction times may be prolonged but show a similar invariance with amplitude as in the normal case (*middle panel*) or contraction times are prolonged and also increase significantly with amplitude (*right panel*).

To quantify the impairment in the speed control of single voluntary contractions that normally keeps contraction times almost constant in individual subjects, the relationship between contraction time as the dependent variable (y axis) and amplitude being the independent variable (x axis) was determined by linear regression analysis of 20 to 30 trials (AM-CT regression). In fig. 3A such a regression line is presented for a normal subject and in 3B for an HD patient (Case 17; *cf.* fig. 2, right side). The slope of the regression line of the normal subject was close to zero, whereas in the HD patient the slope of the regression line was considerably steeper. Furthermore, the scatter of the single trial values around the AM-CT regression line was much larger in the HD patient than in the normal subject.

Each AM-CT regression line can be described by its slope and one reference point (e.g., the intercept). Since some HD patients had difficulties in performing rapid contractions of small amplitude the contraction time corresponding to an amplitude of 2N (CT2N) was chosen instead of the y intercept as reference value. Thus for each subject and patient the AM-CT relationship is characterized by one pair of values: the y value of the AM-CT regression line at 2N (CT2N) and the slope of the AM-CT regression line (AM-CT slope) (*see* fig. 3B).

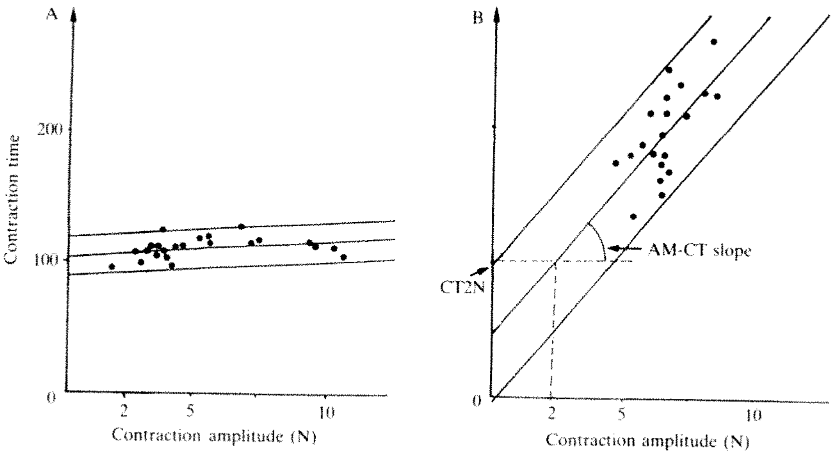


FIG. 3. Linear regression line analysis between contraction amplitude (*abscissa*) and contraction time (*ordinate*). The slope of the regression line (AM-CT slope) is much steeper in an HD patient (B) than in a normal subject (A). In order to display this slope for the different populations examined such regression lines were determined for each subject. They can be expressed by the AM-CT slope and the contraction time at a force level of 2N (CT2N). For the normal subject CT2N = 107 ms, AM-CT slope = 1.7 ms/N; for the HD patient CT2N = 95 ms, AM-CT slope = 24.1 ms/N.

Therefore the AM-CT regression line of each subject can be represented by one point in an x/y plane taking CT2N as the x value and the AM-CT slope as the y value; 95% of the normal values could be encompassed by an ellipse as shown in fig. 4A. When plotting the HD patients against this normal ellipse it appears that all the data points of HD patients lay outside or at the border of this normal range (fig. 4A, triangles on left side). The 2 HD patients at the border of the normal range were only mildly affected (Case 7, 30 yrs, M, DUR = 5; CHOR = 1.5, DIS = 0.3; Case 14, 43 yrs, M, DUR = 5, CHOR = 1.5, DIS = 0.5). Also a high percentage of subjects

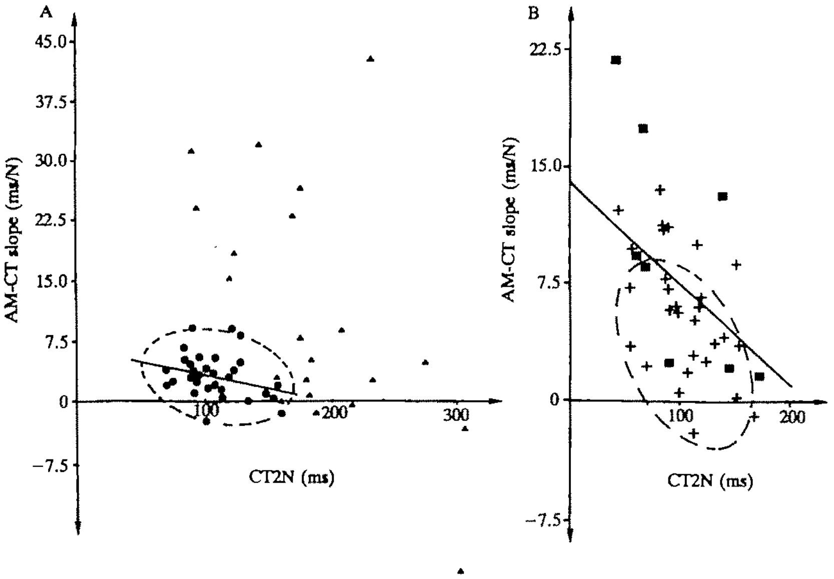


FIG. 4. A, amplitude-contraction time relationship in normal subjects (circles) and in HD patients (triangles). Each data point is derived from an amplitude-contraction time regression analysis in individual cases (as shown in fig. 3) by plotting the slope of the regression line on the ordinate against the value of the regression line for a contraction of 2N on the abscissa. For the normal population an ellipse encompasses 95% of the subjects. Only 2 HD patients lie inside the normal range. B, amplitude-contraction time relationship in individuals at risk without 'soft signs' (crosses) and with 'soft signs' (squares) plotted against the normal ellipse (vertical scale doubled compared with A); 40% of the at risk subjects lie outside this range.

at risk for HD lay outside this normal range (crosses in fig. 4B; squares indicate at risk subjects with 'soft' signs).

Correlation between the increase of contraction time with amplitude and disability. Adopting a criterion of 9 ms/N as the upper normal limit for the slope of the AM-CT relation (Hömberg *et al.*, 1984) the HD patients could be divided into subgroups with normal and abnormal slopes. The mean disability scores for these two subgroups showed a highly significant difference with a mean score of 0.75 ± 0.65 in the HD patients with normal and 1.52 ± 0.47 in those with abnormal slopes. This indicates that the increase in the AM-CT slope was associated with more advanced disease. This was also reflected in a significant positive correlation between the AM-CT slope and the disability score (fig. 5), ($r = 0.47$, $P < 0.05$, two-tailed test).

Contraction time variability. In each subject the scatter of the contraction times around the AM-CT regression line was expressed as the mean value of the absolute distances of individual contraction times from the AM-CT regression line. In normal subjects the mean value of this deviation from the AM-CT relation (CTV) is about 10% of the mean contraction time. The mean value for CTV in normals was 12.8 ± 4 ms. As can be seen in fig. 6A (left side) there is no significant influence of age on CTV in normal subjects (slope = −0.021 ms/yr, r = −0.059, n.s.). In patients with HD, however, (fig. 6A, middle) contraction times vary to a much larger extent than in normals: the mean value of CTV in patients with HD was 55 ± 30 ms, which was significantly larger than in normals ($P < 0.01$). Plotting individual CTV values of HD patients against the normal range revealed only 2 HD patients with a nearly normal scatter of the contraction times around the AM-CT relation. These 2 subjects were already mentioned as having a normal AM-CT relationship. No influence of age on CTV was observed in HD patients (slope = 0.039 ms/yr, r = 0.0128, n.s.). A considerable percentage of people at risk (14/37 at risk subjects) also showed a significantly higher CTV value than the normals (fig. 6A, right side).

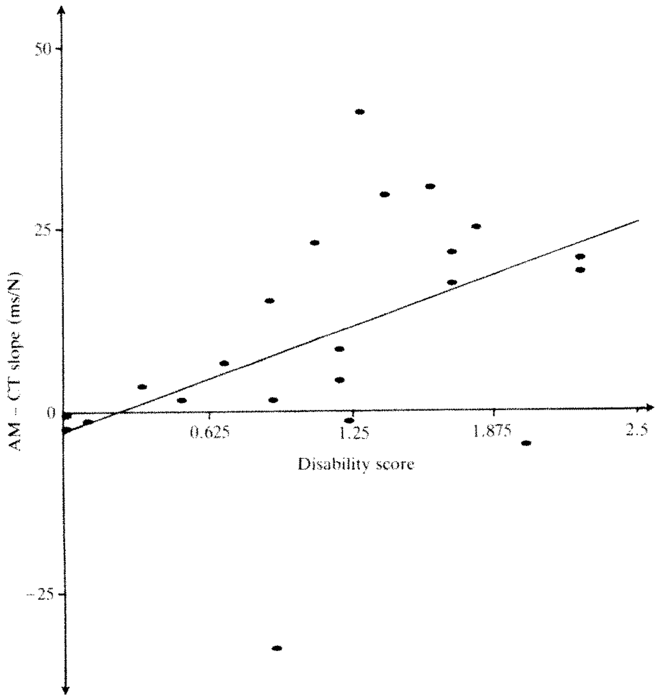
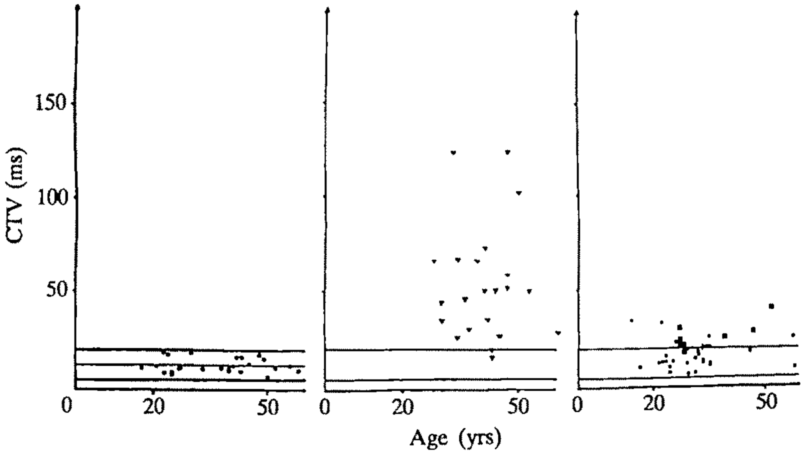


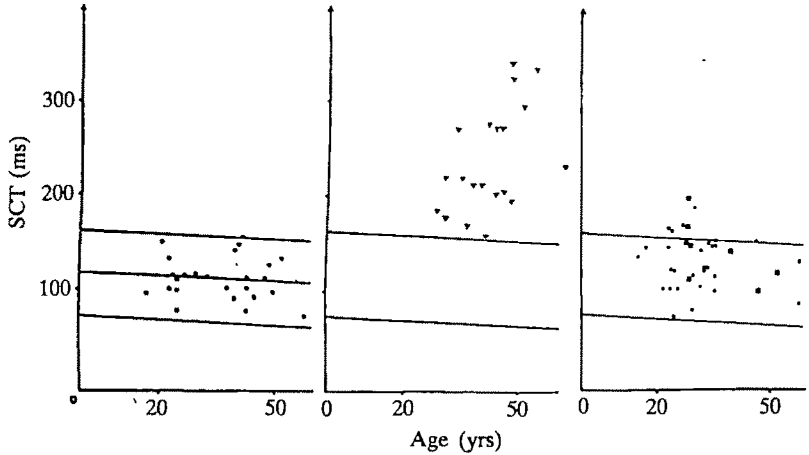
FIG. 5. Relationship between the slope of the amplitude-contraction time (AM-CT) regression line and the disability score. This shows a significant positive correlation, the more affected patients having a larger increase in contraction time with amplitude.

Standardized contraction time. The foregoing calculations have established the basis for the comparison of contraction times between normal subjects and patient groups. Since most of our subjects produced contractions with a mean amplitude of about 5N we selected the point corresponding to the 5N-value of the AM-CT regression line in order to define in each individual a contraction time suitable for intergroup comparisons. This will be referred to as standardized contraction time (SCT). In normal subjects there was no significant effect of age (fig. 6B, left side) (slope = −0.305 ms/yr, r = −0.159, n.s.) on SCT. In HD patients, however, a clear

A Contraction time variation (CTV)



B Standardized contraction time (SCT)



C Reaction time (RT)

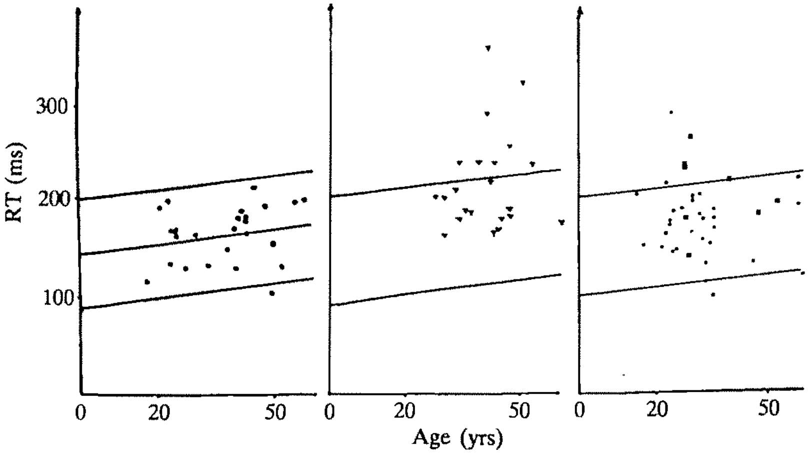


FIG. 6. A, relationship between variation in mean contraction time (CTV) from the individual contraction time-amplitude regression line and age in normals (*left side*), HD patients (*middle*) and individuals at risk (*right side*); squares indicate those with 'soft' signs. B, relationship between standardized contraction time (SCT, taken from individual contraction time amplitude regression lines at 5N) and age in normals (*left side*), HD patients (*middle*) and individuals at risk (*right side*); squares indicate those with 'soft' signs. C, relationship between mean simple reaction time (RT) and age in normals (*left side*), HD patients (*middle*) and individuals at risk (*right side*); squares indicate those with 'soft' signs.

increase of SCT with increasing age can be observed (slope = 3.12 ms/yr, $r = 0.453$, $P < 0.05$) corresponding to the progression of HD with increasing age. The group mean value for SCT in normals was 114 ± 23.7 ms in contrast to a mean value of 217 ± 53.3 ms in HD patients ($P < 0.001$, t test, two-tailed).

Plotting individual SCT values for the patients against the age-related regression of normals revealed that all of the values of the HD patients lay outside the normal range (fig. 6B, middle). In the at risk group, 8 subjects had abnormal results (fig. 6B, right side). This parameter thus separated the disease group most clearly from normals.

Both slowing of contraction times and increase of contraction time variation seem to be early signs for a deficit in the regulation of rapid single voluntary contractions in HD patients and at risk subjects. The influence of disease duration on these parameters will be discussed later, and is summarized in Table 3.

Reaction time. In normal subjects reaction time slightly increases with age (fig. 6C) (slope = 0.545 ms/yr, $r = 0.226$, n.s.). The mean RT value for the normal population is 163 ± 28.1 ms. In patients with HD the mean RT was 252 ± 74.2 ms and thus significantly larger than the normal value ($P < 0.01$). Most patients show reaction times in the upper normal range. Reaction times covary with patient age (fig. 6C, middle) (slope = 3.912 ms/yr, $r = 0.4990$, $P < 0.05$). There are some patients with normal reaction times even with long-standing disease. But only about one-third of the HD patients show RTs which are prolonged by more than 2 SDs beyond the

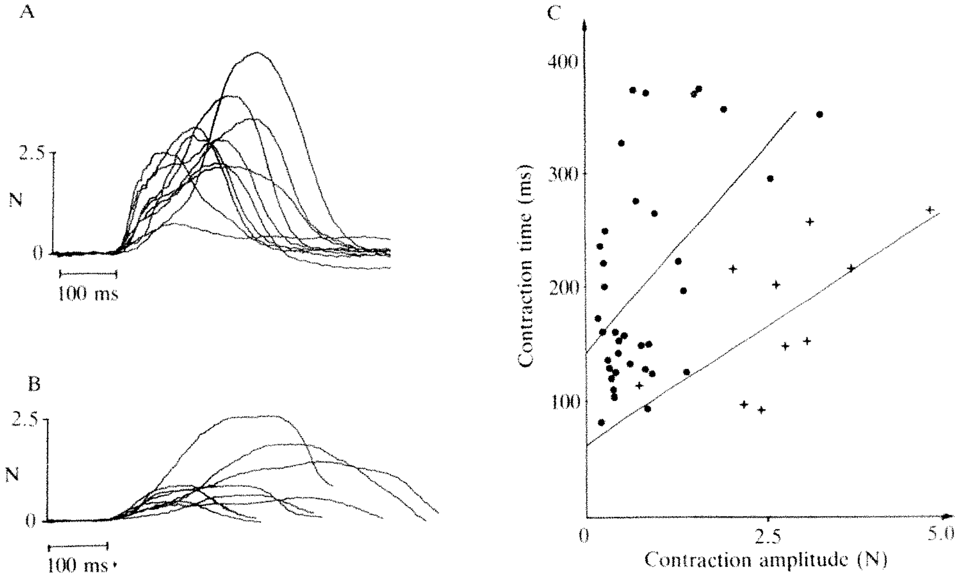


FIG. 7. Comparison between voluntary isometric index finger extensions (A) and involuntary hyperkinetic extensions (B) in a 32-yr-old male HD patient with predominantly distal hyperkinetic movements. Involuntary contractions of comparable amplitude to voluntary contractions have even longer contraction times (C). ● = hyperkinetic contractions, + = voluntary contractions.

normal age-RT regression line. Only 6 of the subjects at risk show prolonged reaction times (fig. 6C, left side). It appears, therefore, that abnormal RTs in HD patients and at risk subjects are rarer than the abnormalities in force production.

Time characteristics of isometrically recorded hyperkinesia. In some HD patients who presented with marked hyperkinesias restricted to the distal upper limbs, we compared their most rapid voluntary contractions with those resulting from involuntary hyperkinesias. A typical example is shown in fig. 7. Voluntary isometric contraction curves (fig. 7A) aligned at onset are compared with involuntary contractions (fig. 7B) in a 32-yr-old male HD patient (DUR = 11, DIS = 1.5). Most of the involuntary hyperkinetic contractions are slower than the voluntary contractions of comparable amplitudes. In fig. 7C the AM-CT relationship of voluntary (crosses) and involuntary (dots) contractions are shown. The AM-CT slope is steeper for the involuntary than for the voluntary contractions. Comparisons between different patients show that with more pronounced hyperkinesias the contraction times also increase and become more dependent on amplitudes.

The EMG pattern of hyperkinesias are illustrated in a 31-yr-old patient with early HD, who presented with low amplitude irregular hyperkinesias restricted to his right toes. Fig. 8 shows recordings of EMG activity from the short toe extensors (EDB) and flexors (FDB) and an accelerometer trace from the big toe. Using a long

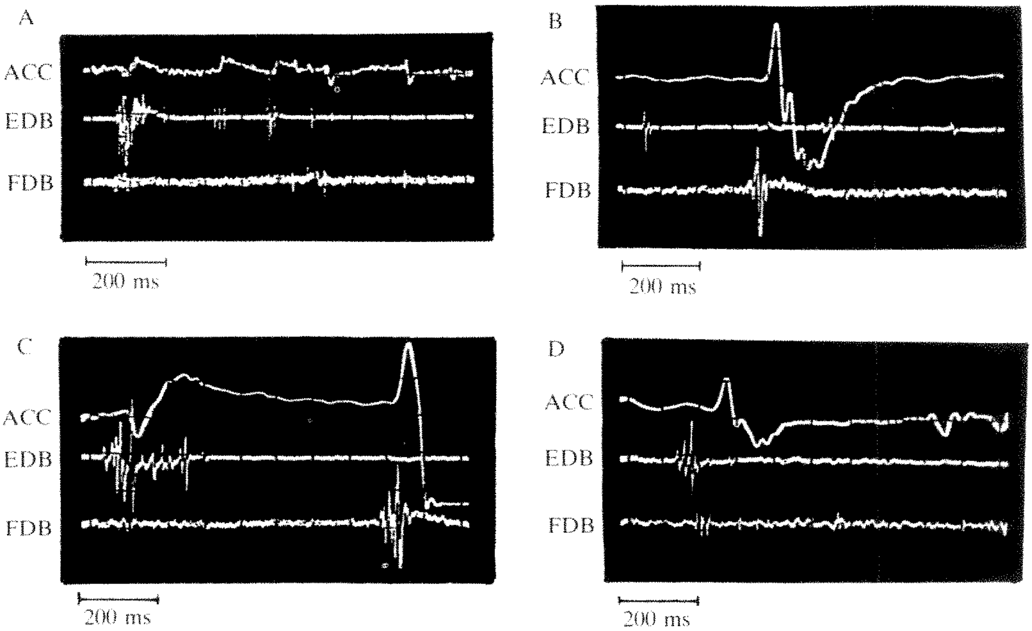


Fig. 8. Different EMG patterns in the extensor digitorum brevis (EDB) and the flexor digitorum brevis (FDB) muscles in a 31-yr-old male subject during hyperkinetic movements of the right toes. The burst durations vary randomly (A, long time constant). Short myoclonic bursts (B) as well as tonic discharges (C) and complex agonist/antagonist patterns (D) may occur. ACC = accelerometer trace.

time base (A) an irregular sequence of EMG bursts of highly variable duration (40–400 ms) is apparent in both muscles. Most bursts are restricted to the EDB but occasionally ordered sequences with an EDB burst followed by an FDB burst may occur (D), whereas coactivation of EDB and FDB is not observed. Therefore, even in early chorea the observation by Hallett (1983) applies, that in chorea a wide variety of different EMG patterns underlie choreic hyperkinesias ranging from short myoclonus-like bursts (as in B) to long 'tonic' discharges (as in C). Occasionally (as in D) ordered sequences of agonist and antagonist can be observed resembling, for example, the 'triphasic' pattern characteristic of fastest voluntary isotonic movements.

Observations in other choreic disorders. A young man (29 yrs, DUR = 6, DIS = 2.25) was studied who suffered from the akinetic Westphal variant of HD. His contraction parameters were the most prolonged of all HD patients studied: his

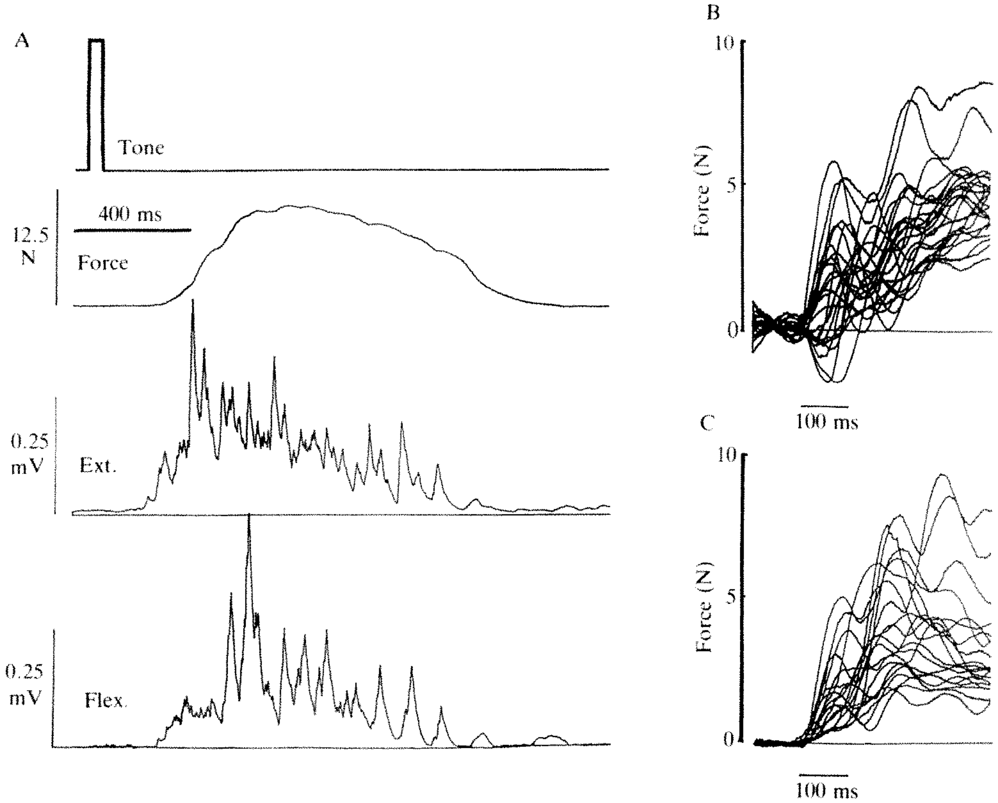


FIG. 9. A, most rapid isometric index finger extension of a 29-yr-old HD patient suffering from the akinetic Westphal variant of HD (note the change of the time scale compared with fig. 1). Oscillations are superimposed on his contractions. These oscillations are similar to those observed in parkinsonian patients. They are consistently found both in patients with tremor at rest (example in B) and in akinetic-rigid parkinsonian patients without tremor at rest (example in C). In all 3 cases a 10–13 Hz action tremor can be observed during the contractions. This kind of action tremor present in the Westphal variant of HD is typical for Parkinson's disease and different from the smoothly slowed shape of contractions observed in HD.

SCT (332 ms) rather underestimates the actual amount of slowing because he was unable to produce most rapid contractions of smaller amplitudes (minimal amplitude 6N). His efforts to produce a most rapid small contraction always elicited series of EMG bursts which he was unable to stop (fig. 9A, left side). Recordings of the most rapid single index finger extensions in patients with PD show a similar action tremor superimposed on the voluntary contractions. Two typical examples are shown in fig. 9B and C. This 10 to 13 Hz action tremor can be observed in PD patients with tremor at rest (fig. 9B) as well as in an akinetic-rigid PD patient without tremor at rest (fig. 9C). Voluntary alternating frequencies of the patient with the Westphal variant were also the slowest observed in this study (2.6 Hz). In contrast to other HD patients his postural tremor was clinically apparent. It showed a higher peak frequency (7.7 Hz) and considerably higher amplitudes. Obvious bursts in the EMG suggested that this tremor was due to neural synchronization. The presence of a synchronized postural tremor and the repetitive EMG bursts superimposed on the contraction curves are two features more typical of PD than of HD.

A 30-yr-old female with Sydenham's chorea due to recurrent streptococcal infections was also studied. All movement parameters showed similar slowing as in HD patients (tremor frequency = 2.8 Hz, voluntary alternating frequency = 3.9 Hz, SCT = 210 ms, DEV = 32 ms, RT = 185 ms ± 49). The slowing of the fastest isometric contractions was caused by a smooth slowing of build-up of EMG activity indistinguishable from the EMG pattern in HD patients.

Alternating Index Finger Movements

The fastest voluntary serial movements. After having presented the analysis of single isometric contractions we will now demonstrate the impairment of voluntary alternating movements in HD. In fig. 10A the acceleration signal of most rapid alternating index finger movements in a normal subject (left side) and that in an HD patient (right side) are presented. The spectral composition of these signals (fig. 10B) shows that the normal subject can move his index finger initially at an alternation frequency of about 8 Hz. After a few seconds the peak frequency gradually declines to values around 4 Hz. The sharp peaks in the spectra indicate that the movement was performed very regularly. In the HD patient, however, the spectra are flat without clear peaks, which reflects the irregularity of the movements. Only initially a clear 4 Hz peak is visible. Compared with the normal subject the maximal alternation frequency is considerably slowed.

Group means of maximal alternation frequencies were 6.77 ± 0.94 Hz for normals compared with 4.91 ± 1.5 Hz in HD patients ($P < 0.001$, Student's t test (two-tailed)). The regression between maximal alternation frequency and age was plotted for the normal population along with 2 SD intervals to define the normal range (fig. 10C). In normals the frequency of the most rapid alternating index finger movements slightly decreases with age (slope = 0.024 Hz/yr, r = 0.258, n.s.) (fig. 10C, left panel). In HD patients there was a clear decrease of frequency with age (slope = 0.087 Hz/yr, r = 0.555, $P < 0.01$). Only 7 out of 21 patients produced the

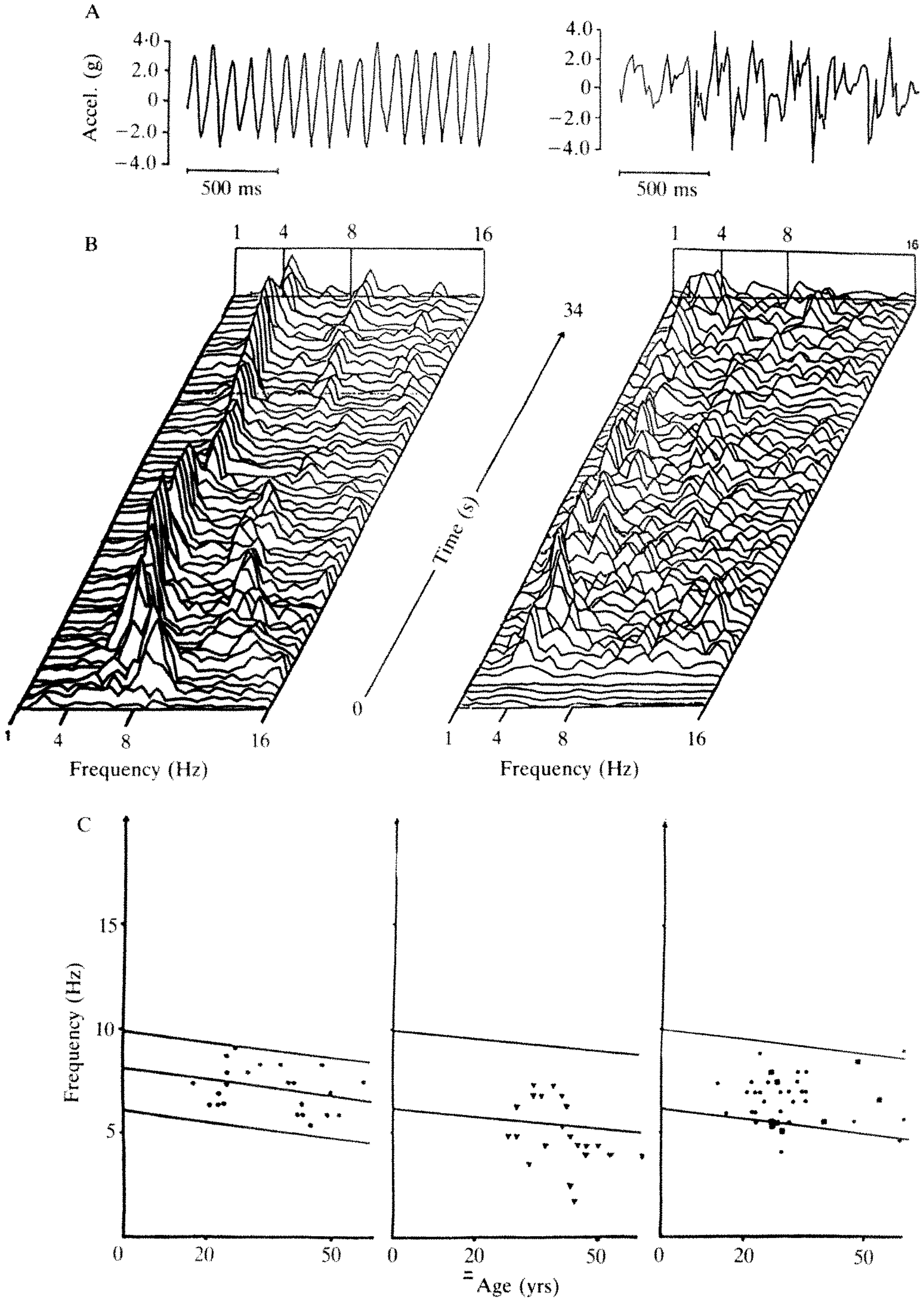


Fig. 10. Accelerometer recordings (A) and power spectra (B) in arbitrary units of most rapid alternating index finger movements in a normal subject (*left side*) and in a patient with HD (*right side*). Over a period of 34 s consecutive partially overlapping spectra are presented. In the normal subject the maximal alternation frequency is at around 8 Hz and drops to 4 Hz after some seconds (*left panel*). The patient with HD is unable to produce regular movements as reflected in the lack of sharp peaks in the spectra. The maximal alternation frequency is decreased to values around 4 Hz. (C), age-related regression of maximal frequency of alternating index finger movements. In normal subjects maximal alternation frequencies decrease with age (*left*). In most of the HD patients (*middle*) and in some of the subjects at risk (*right*) maximal alternation frequencies are decreased. Squares indicate at risk subjects with 'soft' signs.

most rapid movements at an alternation frequency within the normal range (fig. 10C, middle panel). Also in 7 individuals at risk, maximal voluntary alternation frequency was slowed beyond normal limits (fig. 10C, right side).

Since the forearm was not fixed these measurements may be influenced by involuntary movements of the forearm or the whole arm. Single hyperkinetic movements, however, would yield a low frequency spectral component below 2 Hz. Hence interference by single hyperkinetic movements cannot explain the occurrence of peaks in the spectra of voluntary alternating movements in the range between 4 and 6 Hz.

Involuntary alternating motor activity: postural tremor. Analogous to the analysis of single isometric contractions, we recorded not only voluntary but also involuntary alternating motor activity (tremor) in order to examine whether the involuntary alternating tremor movements are slowed in HD. The outstretched hand of a normal subject shows some low amplitude postural tremor (fig. 11A, left side). The frequency spectra of such a physiological tremor are shown from bottom to top for a 25 s epoch on the left side of fig. 11B. The right side of fig. 11B presents the time course of the spectral composition of tremor of a typical HD patient. In the normal subject, spectra are characterized by fairly broad spectral maxima at frequencies around 9 Hz. In contrast, in the HD patient the spectral maxima are shifted to lower frequencies (around 6 Hz). They also show a broad-based peak similar to that in normal physiological tremor. The average peak frequency in the HD group was 5.32±2.25 Hz compared with 8.64±1.13 Hz in the age and sex-matched control group ($P < 0.001$, t test (two-tailed)). To identify abnormalities of tremor of peak frequency in individual cases the age-tremor peak frequency regression of the normal population was computed. As illustrated by the left of the three panels of fig. 10C, peak frequency does not increase significantly with age over the range from 16 to 58 yrs (slope $= 0.011$ Hz/yr, $r = 0.104$, n.s.). In the HD patients, however, there is a clear dependence of peak frequency on age (slope $= -0.146$ Hz/yr, $r = -0.636$, $P < 0.01$). In 14 of 22 patients with HD peak frequency lies below the normal range of peak frequency (fig. 11C, middle panel). Nine subjects at risk had an abnormally low tremor peak frequency (fig. 11C, right panel).

The tremor measurements may have been contaminated by involuntary movements from the nonsupported proximal parts of the upper extremity. With the arm kept outstretched, however, movements around the elbow joint were diminished and the resonance frequency of the whole arm lies certainly below 3 Hz.

Summary of Proportions of Abnormalities Over All Parameters

Table 2 summarizes the incidence of the abnormalities found in HD patients and at risk subjects for the various parameters. It is evident that the measurements of single isometric contractions (AM/CT; CTV) are most frequently impaired whereas tremor peak frequency and peak frequencies of fastest voluntary alternating movements are abnormal only in about two-thirds of the HD patients and reaction times are prolonged only in one-third of all HD patients. A similar distribution of

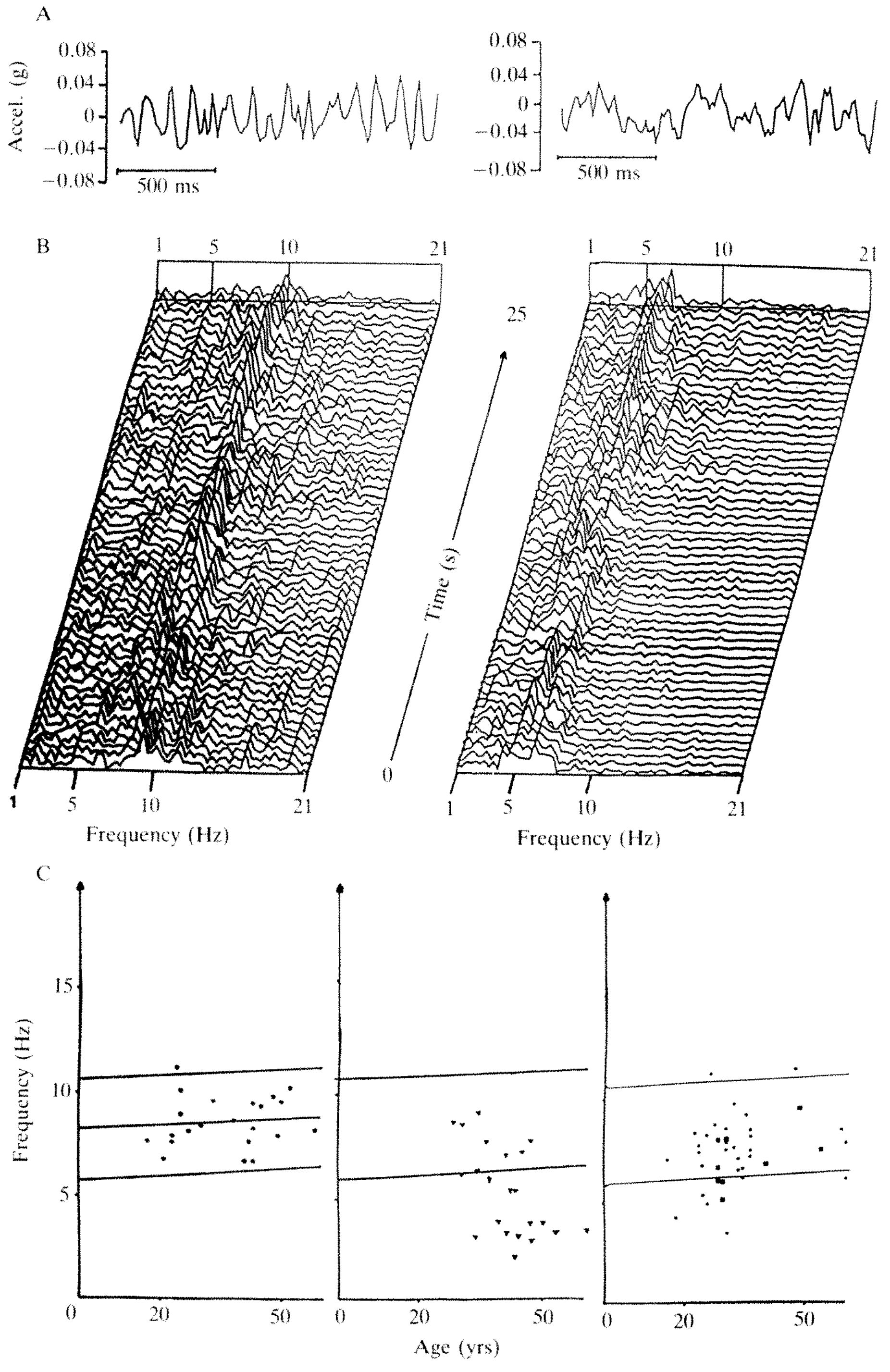


FIG. 11. Accelerometer recordings (A) and power spectra in arbitrary units (B) of postural tremor of the dominant hand recorded over a period of 25 s in a normal subject (*left side*) and in a patient with HD (*right side*); 48 consecutive partially overlapping power spectra calculated from periods of 4.2 s duration are plotted to visualize variation of the spectral composition of the tremor. In the HD patient tremor peak frequency is decreased. (C), age-related regression of tremor peak frequency in normal subjects and normal variation as defined by 2SD above and below the regression line (*left panel*). Most of the 22 patients with HD (*middle panel*) show a tremor peak frequency below the normal range. Also some of the people at risk (*right side*) have lowered tremor peak frequencies. Squares indicate at risk subjects with 'soft' signs.

TABLE 2. INCIDENCE OF ABNORMALITIES OF MOVEMENT PARAMETERS IN PATIENTS WITH HUNTINGTON'S DISEASE (HD) AND RELATIVES AT RISK (HR)

	HD		*HR*	
TRE	14/22	(64%)	9/40	(23%)
VAM	14/22	(64%)	7/39	(18%)
AM/CT	20/22	(91%)	14/37	(38%)
CTV	20/22	(91%)	14/37	(38%)
RT	8/22	(36%)	6/37	(16%)

TRE = tremor peak frequency, VAM = maximal alternation frequency of voluntary alternating index finger movements, AM/CT = increase of contraction time with contraction amplitude, CTV = contraction time variability, RT = reaction time.

abnormal findings across these parameters appears in the at risk group. All percentages observed lie well below the maximal expectable value of 50% gene carriers.

Covariation of Movement Parameters with Disability Score and Disease Duration

The correlation between AM-CT slope and disability has already been described. Furthermore, in the HD patients' other motor parameters and RT have been correlated with disability scores (DIS) and duration of the disease (DUR) (Table 3). Only RT showed a significant ($P < 0.01$) correlation with the disability score. No other parameters were significantly correlated with disease duration.

Association of Motor Parameters with Psychometry in HD

Table 4 summarizes the correlation coefficients of the four psychometric tests and the motor parameters. Except for slight associations of CTV with the Raven and the WIP test and a slight association of the SKT with voluntary alternating movement frequencies and RTs, all other motor parameters did not show any significant covariation with psychometry.

TABLE 3: ASSOCIATIONS (EXPRESSED AS PEARSON PRODUCT-MOMENT CORRELATION COEFFICIENTS) BETWEEN MOVEMENT PARAMETERS AND DISABILITY SCORE (DIS) AND DURATION OF CHOREIC SIGNS (DUR) IN HD PATIENTS

	TRE	*VAM*	*CTV*	*RT*
DIS	−0.3452	−0.2131	0.4021	0.5651**
	(n.s.)	(n.s.)	(n.s.)	
	n = 21	n = 21	n = 21	n = 20
DUR	−0.3940	−0.0734	0.1908	0.1667
	(n.s.)	(n.s.)	(n.s.)	(n.s.)
	n = 21	n = 21	n = 21	n = 20

Abbreviations of movement parameters as in Table 2. ** $P < 0.01$. n.s. = not significant.

TABLE 4. ASSOCIATIONS (PEARSON PRODUCT-MOMENT CORRELATION COEFFICIENTS) BETWEEN MOVEMENT PARAMETERS AND PSYCHOMETRIC TESTS (WIP, MWT, RAVEN, SKT)

	TRE	*VAM*	*CTV*	*SCT*	*RT*
WIP	0.0031 (n.s.) n = 22	0.0847 (n.s.) n = 22	−0.4319** n = 22	0.2045 (n.s.) n = 22	−0.0192 (n.s.) n = 22
MWT	0.0377 (n.s.) n = 23	0.3049 (n.s.) n = 23	−0.3969 (n.s.) n = 23	−0.2750 (n.s.) n = 23	−0.2884 (n.s.) n = 23
Raven	−0.0618 (n.s.) n = 23	0.2437 (n.s.) n = 23	−0.5129** n = 23	−0.1639 (n.s.) n = 23	−0.2629 (n.s.) n = 23
SKT	−0.1687 (n.s.) n = 22	−0.5273** n = 22	0.2797 (n.s.) n = 22	0.1276 (n.s.) n = 22	0.4751** n = 22

* For explanation *see* text. Abbreviations of movement parameters as in Table 2. ** $P < 0.05$. n.s. = not significant.

DISCUSSION

The principal finding of this study is that patients with HD are unable to produce motor activities as fast as normal subjects. As shown by quantitative analysis this disturbance is a consistent feature in HD patients and in a proportion of those at risk for the disease. It affects various types of rapid voluntary motor acts: single isometric contractions and serial alternating movements, as well as the involuntary tremor and hyperkinetic contractions or movements. As all of the subjects at risk and the majority of HD patients were free of any medication that might interfere with motor activity, medication effects can be excluded as a possible cause of this slowing.

In normal subjects rapid single muscle contractions are performed at approximately the same time irrespective of their amplitude (Freund and Büdingen, 1978). This independence of contraction time on amplitude is accomplished by a linear increase of the rate of rise of tension with increasing amplitude. The capacity of the motor system to adjust rate of rise of tension to amplitude is referred to as speed control. This speed control system achieves 'isochrony' not only for the fastest possible contractions or finger movements but also for a wide range of learned 'automatic' everyday movements such as writing (Viviani and Terzuolo, 1980), drawing, typing or even such complex tasks as weight lifting (Enoka, 1983). This stable relationship between contraction time and amplitude is lost in more severely affected HD patients. The more severely affected is the patient, the slower the rapid contractions and the larger the increase in contraction time with contraction amplitude. Thereby the patients lose an invariant feature of motor control.

One possible neuronal mechanism underlying the impairment of the speed control system is the disturbance of firing rate modulation in the final common pathway. The generation of rapid movements requires short high-frequency bursts released from the motoneurons. At the present time there is no information about single unit recordings from HD patients during rapid contractions, but it seems likely that these patients are unable to produce firing rates as high as required for the generation of normal rapid contractions. In PD there is direct evidence from motor unit recordings (Dietz *et al.*, 1974) that the discharge rates are slower than in normals.

The impairment in speed control demonstrated for HD patients in this study resembles the slowing of motor activity that is well documented in many quantitative studies of patients with the more common basal ganglia disorder of Parkinson's disease (Lance *et al.*, 1963; Draper and Johns, 1964; Barbeau and de Groot, 1966; Brumlik and Bosches, 1966; Flowers, 1975, 1976; Hallett and Khoshbin, 1980; Teräväinen and Calne, 1980; Evarts *et al.*, 1981; Baroni *et al.*, 1984). This suggests that slowing of motor activity may be caused by pathological mechanisms common to both basal ganglia disorders. Closer inspection of the fine structure of these abnormalities, however, especially for the fastest contractions, discloses considerable differences. As demonstrated by Hallett and Khoshbin (1980) and Teräväinen and Calne (1980) the EMG records of PD patients performing single rapid voluntary movements are characterized by a lack of increase in the size of the first agonist burst with increasing amplitude and, to compensate for this deficit, by series of subsequent bursts alternating from agonist to antagonist. Analysing the fastest isometric index finger extensions in PD patients with and without tremor at rest in the same way as described here for HD patients, we invariably found oscillations superimposed on the contraction curves caused by repetitive EMG bursts occurring simultaneously in the agonist and antagonist with a frequency of 10 to 13 Hz (Hefter *et al.*, 1985; Hömberg *et al.*, 1985). This kind of action tremor measured under isometric conditions has already been analysed by Lance *et al.* (1963) and probably parallels the oscillations seen in the isotonic recordings of Hallett and Khoshbin (1980) and Teräväinen and Calne (1980). The latter authors also emphasized that these EMG oscillations during voluntary movement were independent of the presence of resting or postural tremors in their PD patients. The changes in EMG activity underlying the slowing of motor activity are different in HD as compared to PD although the resulting slowing as measured by mean values of contraction times may be similar. In HD we find a deficit in building up EMG activity causing prolongation of EMG bursts and slowness of contraction without evidence for tremor such as bursting in the EMG or oscillations superimposed on the force trajectory as in PD.

The comparison between samples of superimposed tremor beats recorded isometrically from the finger of a PD patient and some superimposed finger hyperkinesia of similar force amplitude recorded from a HD patient show that the time course in both kinds of different contractions is nearly the same. Thus the only difference between both kinds of involuntary activity remains that the tremor in PD is regular and hyperkinesia in HD is irregular. An association between the slowing of movement and the occurrence of an abnormally slow tremor of high amplitude is frequently observed in basal ganglia and cerebellar disorders. Cooling experiments in cerebellar nuclei and in the striatum (Conrad and Brooks, 1974; Cooke and Thomas, 1976; Hore *et al.*, 1977; Vilis and Hore, 1980) have shown that the ongoing neural activity is desynchronized in both structures before cooling but becomes slowed and synchronized during cooling. This goes along with the development of coarse limb oscillations. In contrast, neither cooling nor ablating the motor cortex changes the time course of rapid plantar flexions performed by monkeys, but reduces movement amplitude (Rüegg and Juvet, 1984).

In HD the involuntary activity interferes with voluntary activity in an unpredictable way as for the impulses of a random generator. As Wilson mentioned as long ago as 1928, the involuntary movements in HD patients show similarities to voluntary movements, thus resembling 'motor subunits'. Wilson suggested that in HD patients the motor system fails to suppress inappropriate and to select and maintain appropriate movements (Wilson, 1928; Penney and Young, 1983). The results by DeLong and coworkers shed some light on this problem (DeLong and Georgopoulos, 1979, 1981; Crutcher and DeLong, 1984*a*, *b*; Alexander and DeLong, 1985*a*, *b*): analysing single cell recordings in the caudate and putamen in monkeys, they found that the striatum receives a somatotopically-organized input from the motor cortex (*see also* Liles, 1979) and from frontal association and sensory areas. Microstimulation at different points in the putamen led to movements of different parts of the body, caused by contractions of ensembles of several muscles. Thus they observed the activation of 'motor subunits' during their stimulation experiments in the basal ganglia.

A pattern of coactivation between the finger extensor and flexor muscles in the isometric paradigm was consistently observed in all normal subjects, which confirms observations by other authors of similar coactivation in isometric forearm contractions (e.g., Sanes and Jennings, 1984). This pattern was maintained in all HD patients. The onset of agonist activity was followed as early as 20 to 30 ms by concomitant activation of the antagonist muscle. Furthermore, EMG recordings of fastest isotonic elbow extensions and rapid alternating movements at the wrist in HD patients revealed normal triphasic or alternating EMG patterns, respectively. This corroborates observations of normal EMG patterns during voluntary movements made in a few HD cases (Marsden *et al.*, 1983) and in one patient with Sydenham's chorea (Hallett and Kaufman, 1981). The findings indicate that the pattern of activation of muscle groups for simple voluntary movements is preserved in HD patients.

The interaction between voluntary and involuntary contractions in patients with HD was less obvious during larger contractions than during small contractions. By contrast, in PD small amplitude contractions are performed much better than large amplitude contractions. During large amplitude contractions tremulous oscillations inevitably are triggered by the voluntary activity. In monkeys, substantia nigra pars compacta neurons do not show a detectable change of firing rates during small amplitude movements or contractions. However, they change firing rates considerably during large amplitude movements (DeLong and Georgopoulos, 1979; Schultz *et al.*, 1983). Thus deficits in dopamine release are more relevant for large amplitude movements than for those of small amplitude.

Reaction time in HD is impaired to a much lesser degree than the parameters related to actual movement execution. Similar observations have been made in Parkinson's disease (Wiesendanger *et al.*, 1967; Heilman *et al.*, 1976; Evarts *et al.*, 1981). It also fits with the results of single unit recordings in the basal ganglia of monkeys. DeLong *et al.* (1983) studied the relation of neural discharge in various parts of the basal ganglia to different movement parameters and showed that the discharge of these neurons was correlated with movement parameters such as amplitude, velocity and direction. These units fired only during movement execution or just before the mechanographic onset of movement, during which EMG activity builds up. In contrast there was nearly no enhancement of single unit activity in the earlier premovement period and hence no evidence of single unit activity in the basal ganglia related to movement preparation. Our findings also match the effects observed by Horak and Anderson (1984*a*,*b*) of kainic acid lesions or stimulation in the putamen and globus pallidus of monkeys. During rapid arm-reaching movements to a visual target, lesions of the contralateral globus pallidus led to prolonged movement times caused by slowing of EMG build-up, with little or no change of reaction times. On the other hand stimulation of the globus pallidus facilitated speed of movement but left RTs unaltered.

All but one of the HD patients studied did not present with severe rigidity. This stands in contrast to earlier views regarding slowing of movement as a sequel to rigidity (e.g., Walshe, 1955) and is in accordance with Lhermitte (1923), who introduced the term 'syndrome akinetique sans hypertonie' for cases with extrapyramidal symptoms following encephalitis lethargica. Whereas our observations in the patient with Sydenham's chorea were indistinguishable from the findings in HD, the patient with the rigid variant of HD (Westphal, 1883) showed a 'parkinsonian' pattern of bradykinesia as characterized by repetitive oscillations superimposed on the force profile. Furthermore, this patient was the only one presenting with a significantly synchronized postural tremor resembling the postural tremors commonly seen in PD. It therefore appears that the kinesiological and EMG findings in the Westphal variant differ from those in 'typical' HD, but closely resemble those in PD. This finding does also suggest different pathophysiological mechanisms in the Westphal variant.

As dementia is the second major symptom of HD, it has to be considered how far the cognitive dysfunction of the HD patients may have contributed to the pathological motor results obtained. In this respect it is important that reaction times were less abnormal in HD patients than slowing of movement execution. If the cognitive or attentional impairment had caused the observed motor abnormalities, even more prolonged reaction times would have been expected. Furthermore, the slowing of motor activity was observed in a high percentage of individuals at risk not showing any evidence of cognitive impairment and also in some patients in early stages of HD with little or no evidence of cognitive impairment. CTV was the only parameter showing a covariation with the psychometric tests. This is not surprising since CTV is not a pure motor parameter but measures reproducibility, and is probably the reason why it has a better correlation with the Raven than with the MWT test. Finally there was no significant covariation between detailed psychometric data and the other motor parameters except for only marginally significant associations between the frequency of fastest alternating movements, and reaction time for the SKT. This test actually implies motor tasks and reaction time measurements. The bulk of general intelligence tests in both verbal and nonverbal varieties, however, did not show any significant association with the abnormalities of movement parameters. Hence it appears that cognitive impairment as such is not a major factor in the slowing of motor activity observed in this study. Cognitive impairment may aggravate the motor disabilities but does not cause them.

We observed abnormalities of the motor parameters in up to 40% of clinically normal people at risk of developing the disease later in life. This may indicate that the physiological analysis used here can detect preclinical impairment in the motor system in HD and can be used to develop a motor score for early detection of HD (Hefter *et al.*, 1986) but also for therapy control. Experiments can be repeated several times since they are not stressful for the patient. Besides their clinical usefulness, the findings are also pertinent to the understanding of basal ganglia function in motor control. In these very early stages of HD, pathology is restricted to loss of intrinsic neurons in the basal ganglia in contrast to increasing cortical involvement in later stages (Lange, 1981; Lange *et al.*, 1984). Therefore the early stages of HD, in particular, can be regarded as a model for basal ganglia abnormality, which is not caused by a lack of dopaminergic modulation as in PD, but is due to a reduction in the number of intrinsic basal ganglia interneurons and output neurons. In this context the differences in the EMG pattern underlying the slowing of rapid contractions between PD and HD provide information about the different contribution of different circuitry in the basal ganglia on abnormalities of motor control in these two disorders.

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A COGNITIVE NEUROPSYCHOLOGICAL CASE STUDY OF ANOMIA

IMPLICATIONS FOR PSYCHOLOGICAL MODELS OF WORD RETRIEVAL

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SUMMARY

The case of a neurological patient with severe anomic word-finding difficulties is reported. A detailed cognitive neuropsychological investigation of the patient's ability to name objects to confrontation was carried out in an attempt to determine where his cognitive deficits might lie. In contrast to the findings of recent case studies of word-finding difficulty (e.g., Howard and Orchard-Lisle, 1984), it was observed that the patient seemed to have a clear understanding of the items that he was trying to name, suggesting that his problems in word-finding were not semantically based. Indeed, the patient would often generate partial phonological information about the sought-after word, indicating that he had a specific target in mind, and this was reminiscent of 'tip-of-the-tongue' states in normal word-finding. A difficulty in retrieving complete phonological forms of words is considered as the probable locus of his anomia. A distinction is made between semantically-based and phonologically-based anomias.

INTRODUCTION

Patients with anomic aphasia have word-finding difficulties in the absence of major syntactic impairment. Anomia attracted considerable interest from neurologists around the turn of the century, but has only occasionally been discussed within the modern tradition of cognitive neuropsychological research. Our aim in this paper is to present a detailed case report of a severely anomic patient within a cognitive neuropsychological framework, showing how the deficits that the patient exhibits might be explained by a psycholinguistic model of normal word finding.

The word-finding difficulty in anomia becomes particularly obvious when a patient is confronted with an object and required to name it. It is a difficulty that is found regardless of the modality in which the stimulus is presented (Geschwind, 1967). The problem does not seem to reflect an underlying conceptual disorder; objects will be used correctly (e.g., Potts, 1901; Allport, 1983) and their use can be

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described satisfactorily. Bateman (1880) and Potts (1901) showed that their patients were able to reject inappropriate names offered by an examiner and to recognize and accept appropriate ones. The patients could also repeat an object name but it would rapidly be forgotten (*see* Cohn, 1970). This common observation suggests that the difficulty does not stem from any simple articulatory impairment.

Theories of anomia have focused on the distinction between those words that can be produced spontaneously in speech and those that cannot be produced. Perhaps the simplest account of this distinction is considered by Marshall (1977). He constructs a good facsimile of 'anomic' speech from the hundred commonest words in the English language, noting that this set contains almost all the grammatical words and general nonspecific nouns and verbs (such as 'do', 'put', 'thing') that anomic patients use fluently, but few of the specific substantive words that seem to cause the most difficulty. If brain injury could rob a patient of all but the most commonly used words, then the resultant speech could well appear 'anomic'. Marshall's account, however, although descriptively accurate, does not help us to locate where a processing impairment might lie in anomia.

While acknowledging that the words retained in anomia tend to be the commonest in use, Wepman *et al.* (1956) emphasized the generality of meaning of these words. An explanation based on the concept of 'generality of meaning' suggests a semantic deficit in anomia: the patient is unable either to access or to activate the detailed semantic representations of specific nouns (and possibly verbs) and is therefore unable to retrieve the spoken forms of these words. Similar semantic theories have been proposed recently by Allport (1983, 1984; Allport and Funnell, 1981) and by Howard and Orchard-Lisle (1984).

It has commonly been observed, although often only anecdotally, that anomic patients, in some sense, 'know' the word that they are trying to find. This phenomenon may have a parallel in the 'tip-of-the-tongue' state (Brown and McNeill, 1966) in which we feel subjectively that we know the word for which we are searching, indeed may know the initial sound or number of syllables that it has, but cannot quite retrieve it. The claim made by the anomic patient that she or he has a precise word in mind is, however, queried by Geschwind (1967) as possibly epiphenomenal. In line with this view, Goodglass *et al.* (1976) found that the group of anomic patients whom they studied were unable to report with better than chance success either the initial letter or the number of syllables of pictures that could not be named.

In contrast to this finding, we will describe an anomic patient with severe word-finding difficulties who, in naming to confrontation, can often supply phonological information about a sought-after name, in a manner that is reminiscent of 'tip-of-the-tongue' states. We wish to claim that our patient's word-finding difficulties stem from an impairment in activating phonological word-forms. Consistent with this claim, the patient's comprehension of objects that cannot be named appears to be intact, suggesting that his problems in word-finding cannot be attributed to impairment in semantic representations.

CLINICAL HISTORY

As a full medical history of this patient has been given by Kay and Patterson (1985), only a short account is provided here, emphasizing the features that are most germane to the present investigation.

In 1967 the patient, E.S.T., a highly educated man, found himself troubled by unfamiliar difficulties in word-finding and reading that were considered to be the consequence of an invasive left temporal tumour. As a full neurological investigation revealed no immediate life-threatening signs, and as it was felt that a biopsy or exploratory operation might result in neurological deterioration, his condition was simply monitored. In 1976, nine years after the initial diagnosis, his language difficulties had become more profound, and an increase in the size of the tumour revealed by carotid angiography and a CT scan indicated that surgery could no longer be delayed (*see* fig. 1). At operation, a large benign meningioma (11.0 × 6.5 × 6.0 cm) was removed from the lateral ventricle where it was arising from the choroid plexus. Preoperative perimetry of his visual fields had shown a right homonymous hemianopia with sparing of the macula, and no change was observed in visual fields and acuity in postoperative testing. Postoperative assessment of his language abilities in the Speech Therapy Department of Newcastle General Hospital indicated that word-finding and reading difficulties were greater than they had been before the operation. Several years later the patient still suffers from a mild tremor in his right arm and now prefers to write with his nondominant left hand.

E.S.T.'s language abilities were assessed using the Boston Diagnostic Aphasia Examination (BDAE) (Goodglass and Kaplan, 1972) in October 1982. The clinical profile classified the patient as an anomic aphasic, with prominent word-finding difficulty in the context of fluent, grammatically well-formed speech, and auditory comprehension that was relatively intact. Single word repetition was found to be good, but repetition of phrases, particularly those of low probability, was impaired (e.g., *the phantom soared across the foggy heath* → 'the phantom flew over the garden'). Auditory digit span was 4 forwards, 3 backwards. Single word reading was poor: he managed to pronounce only 44.6% of words on the Schonell (1942) graded reading test. In reading aloud single words, he sometimes read phonologically (e.g., *choir* → /tʃɔ/), in a manner that has been held to be characteristic of surface dyslexia (Patterson *et al.*, 1985). He could sometimes demonstrate comprehension of the target word even though it was mispronounced (e.g., *choir* → 'singing'). Written spelling to dictation of single words was also impaired with a tendency for him to produce errors that reflect word phonology (e.g., *sword* → sord).

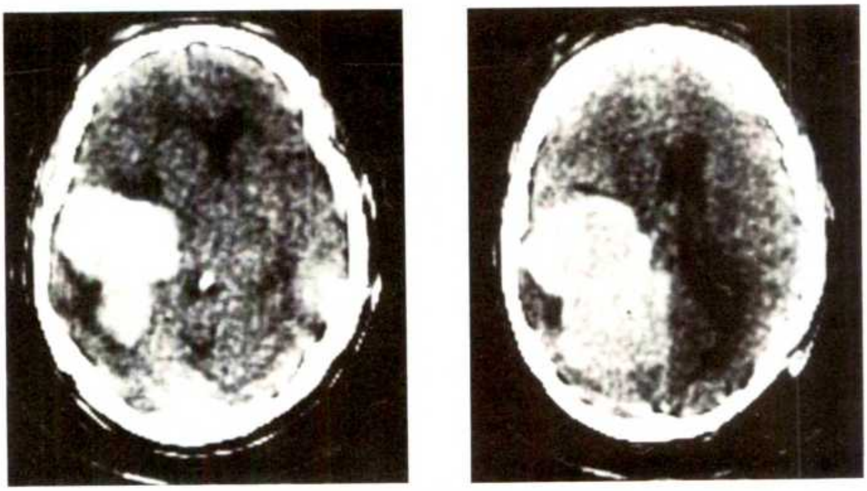

FIG. 1. CT scans of E.S.T. taken one year preoperatively in 1976.

RESULTS

Spontaneous Speech

In spontaneous speech E.S.T. managed quite successfully to mask word-finding difficulties by substituting other more general words, or by producing circumlocutions. His speech was therefore restricted in content, although it was fluent and generally grammatical. A sample of his speech elicited as a description of the 'cookie theft' picture from the BDAE is shown in the Appendix.

Naming to Confrontation

On the Boston Naming Test (Goodglass *et al.*, 1983), E.S.T. was able to name only 22% of the pictures spontaneously. On the remaining occasions the sound of the initial letter of the target was given to him as a phonemic cue. However, he produced the target name in response to the cue in only a further 19% of cases.

We also asked our patient to name the 260 pictures of the Snodgrass and Vanderwart (1980) set; a sample of his responses is shown in the Appendix. He was given unlimited time to name each drawing, but was given a phonemic cue if he failed to produce a response spontaneously or if he started to flounder. He took six 1 h sessions, over as many weeks, to go through the whole set. He named 97 pictures (37%) correctly and without hesitation. A further 27 (10%) were named with some degree of hesitation or after he had worked up to the answer with a string of utterances (e.g., 'five in it, begins with "t", table').

There were 98 instances in which our patient apparently knew little or nothing of the target name and was therefore given a phonemic cue. As before he seemed to be little helped by this knowledge; he went on to name the picture correctly in only 27 cases. Examining his responses after cuing more closely, however, it was evident that even if he could not retrieve the precise phonological form he was sometimes able to take a recognizable guess at it (37/71 cases, e.g., *sledge* → /slʌdʒ/ /slʌg/).

There were also 38 occasions on which E.S.T. failed to name a picture, but on which a phonemic cue was not provided by the experimenter. Although in 16 of these cases he gave either an incomplete response (e.g., *doll* → 'child . . . lady . . . copy . . . false . . .'), or an incorrect name (e.g., *cockerel* → 'hen', *sweater* → 'jacket' [Examiner (E): Are you happy with that?] 'More or less, same sort of thing'), in 22 cases he spontaneously generated phonological information about the target, although he was unable to retrieve a complete form (e.g., *stool* → '/stɒp/, /stɛp/ . . . seat, small seat, round seat, sit on the . . . sit on the . . . /stə/ . . . aye, there's five in it . . . seat, that can't be . . . /stə/ /stip/ /stoon/ . . . It's /stool/ . . . /stei/ /stit/').

Our description of E.S.T.'s performance in spontaneous speech and in naming to confrontation, given in some detail, provides a flavour of the particular difficulties which he faces in these tasks. Later sections will be given over to our attempts to pinpoint the locus or loci of these difficulties.

Picture Recognition and Comprehension

In attempting to name a picture or object, E.S.T. generally indicated that he was aware of what the stimulus represented by setting his responses in a semantic context (e.g., *snowman* → 'It's cold, its a man . . . cold . . . frozen'). However, his ability to use conceptual knowledge constructively was tested using tasks of picture categorization and picture association. The tasks involved either card-sorting or picture-pointing, but did not require a verbal response.

Picture categorization. E.S.T. was asked to reorder random mixes of picture cards into two semantic categories, e.g., *musical instruments* vs *tools and implements*. Since it may be possible to determine the semantic category of an object of the basis of visual attributes alone, several category sets were chosen on the assumption that correct performance on items of these sets requires specific semantic knowledge rather than information about visual or structural characteristics, e.g., *objects from inside the house* (iron, rolling pin, hanger, etc.) vs *objects in the garden* (barrel, garden fork, clothes-peg, etc.). E.S.T. carried out the sorting tasks effortlessly and with only one error: he failed to recognize a *fox*, which should have been assigned to the category of *wild animals*, saying, 'If it's a dog, then it's here', and placing it in the *domesticated animals* pile.

Picture association using real-world knowledge. In this test the patient is required to find a conceptual link between two pictures that must be derived from real-world knowledge. Thus as an example, the patient is shown a picture of a *pyramid* and must point to a picture of a *palm tree* rather than a *pine tree*, on the grounds that 'both are found in hot climates' or 'both are found in Egypt'. Although the target and distractor were selected from the same semantic category, this was not necessarily the case for stimulus and target. Given 52 such triads (devised by D. Howard; personal communication), our patient made only 3 errors, which is within the normal range (normal subjects make 3 errors or less).

Picture association using functional knowledge. In this test the patient is required to find a conceptual link between two pictures that must be derived from functional knowledge (in this case, knowledge that objects occur in the same situational context). Thus the patient is shown a picture of a *kennel*, for example, and must point to a picture of a *dog* rather than a *cat*. As with the previous test, the target and distractor were selected from the same semantic category, although this was not usually the case for stimulus and target. Our patient made no errors on 12 of such triads.

E.S.T.'s processes of picture recognition and comprehension were sufficiently well preserved for him to produce an almost errorless performance on these tasks. While it is clear that semantic category information can be maintained when more specific semantic knowledge is unavailable (thus Warrington's (1975) visual agnosic patients with impairment of picture comprehension were able to carry out superordinate categorization with reasonable success), successful performance on the tests of picture association that we have described would seem to require more precise conceptual knowledge. On the basis of these tests, we conclude that, like the patient described by Howard and Orchard-Lisle (1984), our patient's difficulties in word finding cannot be attributed to failure either in perceptual recognition or conceptual understanding.

Comprehension and Processing of Word Meanings

As we recorded in the Introduction, recent reports of naming disability have concluded that the patient's difficulty lies in deriving a precise lexical semantic specification before accessing a phonological word-form (Howard and Orchard-Lisle, 1984) or in translating between a conceptual/semantic representation and a corresponding word-form (Allport, 1983, 1984). In this section, we report on our attempts to find whether either of these proposed impairments may be responsible for the word-finding difficulties of our patient.

That E.S.T. had detailed conceptual knowledge of common objects was demonstrated by his capable performance on tests of picture association and categorization reported above. We went on to test his ability to carry out word-picture matching and word association tasks which depend on translation between specific lexical codes and underlying conceptual/semantic representations.

Initial word-picture matching tests indicated that E.S.T.'s auditory comprehension of concrete high-frequency items was extremely good, although his ability to understand both abstract and unusual items was somewhat impaired. Thus on the four-choice word-picture matching test of T. Shallice and J. McGill (unpublished), he was 97% correct in selecting the picture to match a concrete word (his single error was on the low-frequency item *rosary*), but 60% correct on abstract words (e.g., *boredom*) and only 33% correct on abstract emotional words (e.g., *agony*). Chance performance is 25% correct. On the Coltheart synonym matching test (unpublished), he was able to match concrete word pairs (e.g., *magazine-journal*) without error, but was only 83% correct in matching abstract pairs (e.g., *origin-source*). Chance performance is 50% correct. Thus it appears that our patient has difficulty in processing the meaning of abstract words. However, such a difficulty is not of primary concern to us; the thrust of the present work is whether his difficulty in naming simple objects and pictures can also be attributed to a central semantic problem.

The tests next to be described all made use of pictures of everyday objects. Note that the order of difficulty of the tests was such that precise semantic judgements were required for successful performance.

Spoken word-picture matching. In the first test, 25 sets of black and white photographs were selected from different semantic category sets such as *fruits* or *vegetables* (*Photographic Teaching Materials*, 1980). The four photographs in each set were semantic coordinates, but were visually dissimilar (e.g., *pineapple*, *grapes*, *lemon*, *pear*). Their names were also phonologically and orthographically dissimilar. One target was chosen arbitrarily from each set; the remaining photographs served as distractors. Note that in an earlier, elicited naming task, E.S.T. had only been able to name 13 out of the 25 targets correctly. For each set the experimenter spoke the name of the target and E.S.T. was asked to point to the correct photograph. In contrast with his naming performance, he made no errors on this task.

In a second test, E.S.T. was given an alternative version of the 'Palm Trees and Pyramids' test described earlier. In this version the patient has to make a real-world association between a spoken word (e.g., *pyramid*) and one of two pictures (either a *palm tree* or a *pine tree* in this case). He made errors on only 2 of the 52 triads (normal subjects make 3 errors or less): 'windmill' was matched with a picture of a daffodil rather than a tulip, 'stethoscope' with a tongue rather than a heart. These errors were also made on the picture triad version.

In a third test of spoken word-picture matching, E.S.T. was required to match a word to one of two line-drawings from the Snodgrass and Vanderwart (1980) set that he had been unable to name successfully. The two pictures were close semantic coordinates like *horse* and *donkey*. He made no errors in selecting the correct picture from 16 of such pairs. The subset of pictures that were chosen for this test were familiar items with relatively high-frequency names. Even though E.S.T. had previously been unable to name them, he had been able on occasion to retrieve some phonological information about the target and it is possible that this was sufficient to allow him to distinguish between the alternatives in the present case. However, there were a number of items in the Snodgrass and Vanderwart set which he had been unable to name and of which he had reported no phonological information. It seemed possible that a semantic difficulty might be the cause of these naming failures. Thus 16 further picture pairs were chosen about which he had had no idea of word structure in naming to confrontation. The pairs were again closely semantically related (e.g., *asparagus* and *artichoke*) and he had to match one of them to a spoken word. He made one error on this task, pointing to the picture of a *wheel* when the experimenter said 'wagon'. We consider, however, that there are reasonable grounds on which to dismiss this as an error of miscomprehension: E.S.T. was reluctant to accept the correct picture as depicting a wagon and, according to the Snodgrass and Vanderwart (1980), so were the majority of normal subjects that they tested since there was little agreement as to the name of the picture; alternative names were cart, wheelbarrow or carriage. Moreover, E.S.T.'s choice depicted a wagon wheel and may have been chosen by default. On naming to confrontation immediately afterwards, he failed to name any of the pictures correctly.

Written word association. In reading aloud E.S.T. often produced incorrect, but phonologically appropriate renderings of written words. At the same time, however, he often demonstrated that he had correctly understood the target word (*see* Kay and Patterson, 1985). Because of these acquired reading difficulties, the majority of lexical comprehension tasks were carried out using spoken words. However, we also gave him 16 sets of written word triads in a test designed by Funnell (1983). In each set, two of the words, matched for lexical frequency and syllable length, are closely related in meaning (e.g., *nail*, *screw*). A third is more closely related to one of these words than the other (e.g., *tack*). Given this word, the patient has to select between the alternatives for the associate that is closer in meaning (e.g., *tack-nail*). E.S.T. was required to make his responses without sounding out any of the words. In a second version of this task the stimulus word was spoken and E.S.T. had to mark the written word associate. Although slow to respond (presumably because of his reading disability), he made no errors on either of these tasks.

'Is this a . . .?' Howard and Orchard-Lisle (1984) showed that although their severely aphasic patient J.C.U. would usually accept the correct name of a picture (and reject incorrect unrelated names), she would also accept the name of a close semantic coordinate on over 50% of occasions on which it was used as a prompt by the experimenter ('Is this a tiger?' to a picture of a lion). A similar test was given to E.S.T. He was shown 40 pictures from the Snodgrass and Vanderwart (1980) set and asked, 'Is this an *X*?', where *X* was the correct name on half of the trials and the name of a close semantic coordinate on the remainder of trials. After practice with 6 items, he was given the experimental pictures in random order. He replied quickly, making only 2 errors: 1 was an initial failure to recognize the picture of a *balloon*, which he immediately corrected (E: 'Is this a balloon?' E.S.T.: 'No, aye, thinking these were just lines'); the second was a failure to accept a correct name, *scarf* (E: 'Is this a scarf?' E.S.T.: 'No, wrap it round your neck'). All the semantic distractors, however, were rejected without hesitation.

On the basis of this selection of semantic comprehension tests, we conclude that E.S.T. has a good understanding of objects and their names, with semantic information that is sufficiently precise to allow him to distinguish between close semantic associates in tests of word-picture matching and word association, and to prevent him from accepting semantically related names in lieu of the correct word.

Auditory Word Discrimination and Repetition

The majority of semantic comprehension tests described above involved auditory word recognition. As E.S.T. performed at a high level on these tests we assumed that this function is well preserved. However, since Allport (1984) reported that patient A.L. was poor at detecting slight mispronunciations, we decided to carry out a systematic investigation of E.S.T.'s ability to make auditory word discriminations.

We recorded in an earlier section that E.S.T. sometimes produced a phonological approximation to the target word in naming to confrontation (e.g., *envelope* → /æmbilꝏp/, *thimble* → /θʌmbl/). We selected 30 of these responses (11 monosyllabic, 11 disyllabic and 8 trisyllabic utterances). E.S.T. was then shown 30 pictures and each one was named by an experimenter. He was asked to say whether the spoken name was correct. On half of the occasions the name was correct; for the remainder the name was a close phonological approximation. In a subsequent test session a week later, the test was repeated using the same stimuli but reversing the manipulation, so that over the two test sessions each picture was named by the experimenter both correctly and with a slight mispronunciation.

E.S.T. accepted the correct name and rejected the inappropriate name for 27/30 pictures. Both the correct name and the inappropriate name were accepted for a further 2/30 (pumpkin → /pʌmpkil/, thimble → /θʌmbl/). In the one remaining case he accepted the correct name 'turtle', but in response to the name '/tɜnə/', he replied 'tortoise would be better'! With a hit rate of 1.0 and a false alarm rate of 0.07, d' is 7.50. Thus although E.S.T. makes a small number of errors on this task, we claim that his perception of single spoken words is well preserved and certainly more intact than his spoken word production.

Auditory repetition of single words is also generally good, with only 4/78 errors on the Coltheart *et al.* (1979) list. He made no errors on a list of 10 monosyllabic words and a single error on each list of 10 two-syllable and 10 three-syllable words. Repetition of one, two and three-syllable nonwords was slightly worse (9/10, 4/10, 6/10 respectively). Errors on both words and nonwords were phonemic paraphasias.

In a further test of auditory repetition, we asked him to repeat the names of the subset of 50 pictures from the Snodgrass and Vanderwart (1980) set that he was unable to produce, and about which he had apparently no phonological information. We also asked him to repeat 50 nonwords constructed from the words by changing one or more consonants. In one session he was given 25 of the words together with 25 nonwords derived from the remainder of the word set. In a second session a week later he was given the other 25 words and the nonwords derived from the first set. Words and nonwords were presented in blocks. At the end of each session, after an irrelevant intervening task, he was given 25 pictures to name (whose names corresponded with the names from which the nonwords in that session had been derived).

Although in the initial confrontation naming task, he had been unable to produce any of the names spontaneously, in auditory repetition of the same names he made only 7/50 errors (including 3 pronunciation errors that he then corrected). As before, he made significantly more errors in nonword repetition: 20/50 errors with only one self-correction. The difference in performance between the two sets of stimuli was significant ($\chi^2(1) = 8.57$; $P < 0.005$). Errors were phonemic paraphasias. In the subsequent test of naming to confrontation, he named only 7 of the pictures correctly.

Determinants of Word Retrieval Success

In this section we return to E.S.T.'s performance in naming to confrontation to take a detailed look at some of the factors which influence his ability to retrieve a phonological word-form successfully and, in cases in which retrieval is unsuccessful, the nature of phonological information that he is able to recover.

It is clear that naming to confrontation is impaired regardless of the modality in which stimuli are presented. Thus on the Coughlan and Warrington (1978) test, E.S.T. named without hesitation 6/15 objects presented visually, 6/15 objects presented tactually and 5/15 objects to description.

It is also clear that this disability is not merely confined to producing common nouns. We compared E.S.T.'s performance in naming common objects with that of naming simple actions which were matched on the frequency of occurrence of their names. Thus we gave our patient 22 photographs that are designed to elicit the present participle form of common verbs (*Photographic Teaching Materials*, 1980). Two measures of frequency of occurrence of the forms were taken using the Francis and Kucera (1982) norms. One was the simple frequency of the '-ing' form of the verb ($\bar{X} = 25.6$). The other was the combined frequency of all words containing the verb stem ($\bar{X} = 199.4$). Two sets of line-drawings of objects were then selected: the first was matched to the action verbs on the simple frequency of their names ($\bar{X} = 22.5$); the second set was approximately matched on the combined frequency of their names ($\bar{X} = 119.1$). Each of the picture sets was given in turn to E.S.T., in a blocked design, and he was simply asked to name the action ('He is yawning') or the object ('It's a whistle'). If he failed either to name the picture immediately, or to generate phonological information indicating that he had a specific target in mind, he was provided with the first sound as a cue. Table 1 illustrates the number of correct responses (either produced immediately by the patient, or after a self-generated cue, or after a phonemic cue had been given by an experimenter), and the number of naming failures on each set. As the Table shows, he was marginally better at naming objects than actions matched on combined frequency of occurrence of their names (both with an immediate

TABLE 1. NAMING ACTION VERB AND COMMON NOUN PICTURES

	Naming successes			
	Immediate	*After own cue*	*After E cue*	*Naming failures*
Action verb pictures (n = 22) e.g., *drying*	11	1	3	7
Common noun pictures (n = 22) (matched on -ing form of verb) e.g., *ear*	7	5	5	5
Common noun pictures (n = 22) (matched on combined frequency of verb forms) e.g., *bed*	12	5	2	3

response and after a phonemic cue). A χ^2 test, comparing correct responses (either produced immediately or after cuing) and incorrect responses on each set, indicated that there were no significant differences between the sets with these measures ($\chi^2(2) = 2.08$).

For each experimental set, it was observed that correctly-named items were higher in frequency than those that could not be named correctly. To find whether lexical frequency of target names is indeed a significant factor in word retrieval we carried out a post hoc analysis of E.S.T.'s responses to the object pictures of the Snodgrass and Vanderwart (1980) set. His responses to this set fell neatly into six categories: (1) where the response was immediately correct; (2) where he had given the correct response after hesitating, or after a few other utterances; (3) where, after an unsuccessful search for the word, a phonemic prompt given by an experimenter elicited a correct response; (4) where he failed to produce a correct response but could supply phonological information about the target; (5) where a phonemic prompt given by an experimenter failed to elicit a correct response but a phonological approximation to the target was produced; and (6) where he failed to produce a correct response or a phonological approximation, either spontaneously or after a cue given by the experimenter.

The lexical frequency of each object name in each category was determined using the Francis and Kucera (1982) norms. Mean frequencies for each category are given in Table 2. As the Table clearly shows, the names that E.S.T. could retrieve (Categories 1, 2 and 3) are higher in frequency than those for which he could only generate partial phonological information (Categories 4 and 5), and those for which he was unable to provide a response (Category 6). A series of Mann-Whitney

TABLE 2. MEAN LEXICAL FREQUENCIES OF OBJECT NAMES IN EACH OF THE SIX CATEGORIES OF RESPONSE IN NAMING PICTURES OF THE SNODGRASS AND VANDERWART (1980) SET*

		*Mean F-K** frequency*	*SD*
1. Immediately correct	(n = 97)	82.5	132.4
2. Correct after delay	(n = 27)	38.0	56.9
3. Correct after E cue	(n = 27)	27.8	36.6
4. Self-generated phonological approximation	(n = 22)	13.6	18.2
5. Phonological approximation after phonemic cue	(n = 37)	7.9	14.2
6. Incorrect	(n = 50)	16.3	23.5

* Mann-Whitney tests indicate that Category 1 differs significantly from all other categories. Category 2 is significantly different from Categories 3, 4, 5 and 6. Category 3 is significantly different from 4, 5 and 6. Categories 4, 5 and 6 do not differ significantly. Level of significance is 0.025.

** Francis and Kucera (1982).

tests carried out on the data provide statistical confirmation of these observations, except for the finding that names produced immediately, or after a delay, were significantly higher in frequency than those produced correctly after an experimenter cue (e.g., Category 2 vs Category 3: $U = 488$; $z = -2.00$; $P < 0.025$, one-tailed). Names produced correctly after an experimenter cue were, however, higher in frequency than those that could not be produced (e.g., Category 3 vs Category 6: $U = 439.5$; $z = -2.52$; $P < 0.005$, one-tailed).

Effects of Incorrect Phonemic Cuing

Various researchers have reported that supplying the anomic patient with phonological information about the sought-after word often precipitates its retrieval (e.g., Howard *et al.* 1985). Interestingly, Howard and Orchard-Lisle (1984) reported that patient J.C.U., who was considerably helped in confrontation naming by the provision of a phonemic cue, could also be induced to produce a semantic coordinate of a pictured object in response to the initial sound of the coordinate. We investigated whether E.S.T. would behave in a similar fashion. Twelve pictures were chosen from the Snodgrass and Vanderwart set that he had successfully named and a further 12 that he had been unable to name. He was given these pictures in random order and again asked to name them. If the target was not produced spontaneously, he was given a phonemic cue. This was not the initial sound of the target, however, but that of a close semantic coordinate. Our patient was able to name 50% of the pictures spontaneously. He was never, however, spurred to produce semantic paraphasias for the remainder. In fact, he became quite frustrated by the misleading prompt: given a picture of a *baseball bat* and the cue, 'It's a /rə/' (for *racquet*), he said, 'Doesn't begin with that though, does it? It's a /bə/!'

Although giving our patient a correct phonemic cue often failed to help him to retrieve the full phonological form of the target, he was frequently able to retrieve some phonological information. Thus on just over half of the instances in which he was given a cue but could not supply the target, he produced a response or responses that approximated to it (37/71 or 52% of cases). There were also 22 instances in which he could spontaneously retrieve partial phonological information but not the whole form. In combination, therefore, there were 59 pictures that E.S.T. was unable to name but was able to recover some information about target word phonology. Not counting repetitions, he produced 170 phonemic paraphasias in total (a mean of 2.9 attempts per picture).

DISCUSSION

Our investigation of E.S.T.'s linguistic capabilities suggests that his anomic pattern of speech production is not due to any impairment of the conceptual or semantic representations of the words that he cannot produce. E.S.T. may have a semantic problem with abstract or emotional words, but extensive testing has failed to reveal any impairment whatsoever to his knowledge of the meanings of words that he has great difficulty in retrieving for output. He did not choose incorrect semantic associates in word-word or word-picture matching, he rejected associated words when offered by the experimenter as possible object names, and he correctly matched words and pictures by association.

While we are convinced that E.S.T.'s anomia was not due to semantic impairment, we are not suggesting that semantic deficits are never a cause of anomic word-finding problems. We would suggest, however, that semantically-based anomias may have somewhat different properties from E.S.T.'s type.

Evidence increasingly indicates that semantic deficits can be specific to certain semantic domains, bringing with them domain-specific naming problems (e.g., Warrington, 1975; Hart *et al.*, 1985). Another feature of semantic impairment is that it appears to affect comprehension and production equally. The patient has difficulty comprehending words that he or she is unable to produce (e.g., Allport and Funnell, 1981; Allport, 1983; Howard and Orchard-Lisle, 1984). This suggests that while there may be separate input and output lexicons for word recognition and production, one system of semantic representations may serve both comprehension and production. The close association that has been observed between degrees of semantic impairment in comprehension and production would support this proposal (Gainotti, 1976; Gainotti *et al.*, 1981; Butterworth *et al.*, 1984).

E.S.T., in contrast, had no difficulty recognizing or comprehending words he could not produce successfully. There was also no hint of domain-specificity in his anomia. He had roughly equal difficulties with all the semantic categories represented by the Snodgrass and Vanderwart (1980) pictures, and we have shown that his anomia extended to verbs as well as nouns.

E.S.T. appears, then, to embody a type of anomic deficit that is not semantic in nature. Many models of speech production postulate some form of phonological lexicon from which the phonemic representations of words are retrieved in response to input from the semantic system. In some models the lexicon in question is specific to speech production (e.g., Morton and Patterson, 1980), while in other models it also plays a role in auditory word recognition (e.g., Allport and Funnell 1981; Allport, 1984). Common to both types of model is the assumption that each word in the speaker's expressive vocabulary is represented by a separate word-form, an entry or a node, in the phonological lexicon.

We propose that E.S.T.'s word-finding difficulty should be understood in terms of a deficit in activating spoken word forms in a phonological (output) lexicon. The discovery that frequency-of-usage affected E.S.T.'s probability of successful word retrieval is certainly compatible with such a proposal because there are several other lines of evidence converging on the suggestion that retrieval from the phonological (output) lexicon is frequency-biased (Ellis, 1985).

We suggest that semantic and phonologically based anomias may be associated with rather different patterns of performance on a variety of psycholinguistic tasks. Thus impairment at a semantic level may manifest itself by: (1) failure or poor performance on semantic categorization tasks or on tasks which require precise semantic knowledge (without a verbal response); (2) improved naming performance with a correct phonemic cue, but also an increased production of semantic paraphasias after phonemic *miscuing*; and (3) no evidence of 'tip-of-the-tongue' responses indicating partial knowledge of the target. In contrast, impairment at a phonological level may be characterized by: (1) good performance on tests of semantic knowledge; (2) a weak effect (if any) of a correct phonemic cue, but no effect of phonemic miscuing; and (3) 'tip-of-the-tongue' responses in some cases.

Our characterization of E.S.T.'s deficit in terms of an impairment in accessing items in the phonological lexicon implies that we believe that the entries themselves may not have been impaired. E.S.T. sometimes retrieves names successfully after extensive effort (e.g., the word *axe* in the Appendix) and may retrieve a name in one session which he was unable to locate in a previous session. Both these observations suggest a retrieval deficit. A more formal argument may be assembled from the fact that E.S.T. showed a superiority for words over nonwords in auditory-vocal repetition, even when the words were ones he can rarely, if ever, access voluntarily in spontaneous speech or confrontation naming. This word superiority effect suggests that lexical phonological entries for such words can in fact function in response to this type of stimulus and can contribute to successful word repetition performance.

If E.S.T.'s verbal semantic system is intact (at least for concrete words), and if his phonological lexicon is also (*ex hypothesi*) intact, then our explanation effectively becomes one of partial disconnection between the two systems. We wish to claim that this disconnection is expressed in terms of weak or fluctuating levels of activation between corresponding representations in the semantic system and phonological lexicon. Semantic representations of words that E.S.T. has used a great many times may still fully activate their lexical phonological entries since frequently-used words have resting levels of activation which are already high (*see* Stemberger, 1985). The same rate of activation may not, however, be sufficient to achieve the necessary level for the production of lower frequency words, even though they may attain a level of partial activation that may allow a phonological approximation (or target-related neologism; *see* Ellis, 1985; Miller and Ellis, 1986) to be generated.

Finally, if the same phonological lexicon as is used in spontaneous speech is also employed in reading aloud familiar words, the proposed deficit could also explain E.S.T's acquired reading disorder (*see* Kay and Patterson, 1985, and Margolin *et al.*, 1985, for similar observations linking anomia with acquired dyslexia). E.S.T.'s errors in reading aloud were a mixture of phonological approximations or neologisms (e.g., *shampoo* → /ʃægən/, *steak* → /skeɪp/) and 'regularization' errors where irregular words were pronounced as if they were regular (e.g., *foot* → /fut/, *break* → /brik/). The advantage for regular words over irregular words that comes with this mode of sublexical phonological reading was evident if his final attempts at words were examined but not in his initial attempts. Comprehension of written words was often good, whether they were read aloud correctly or incorrectly. What seems to have been happening is that E.S.T.'s first attempts at reading words aloud were always lexical but were marred by the same difficulty accessing the phonological lexicon as affects his speech production. Errors at this stage are phonological approximations and there is no regularity effect. When the lexical strategy fails, E.S.T. switches to a sublexical mode, resulting in regularization errors, but also in more successful attempts at pronouncing regular words (and hence a significant regularity effect).

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APPENDIX

A Sample of E.S.T.'s Description of the 'Cookie Theft' Picture

Er . . . two children, one girl one male . . . the . . . the girl, they're in a . . . and their, their mother was behind them in in, they're in the kitchen . . . the boy is trying to get . . . a . . . er, a part of a cooking . . . jar . . . He's standing on . . . the lad, the boy is standing on a . . . standing on a . . . standing on a . . . I'm calling it a seat, I can't . . . I forget what it's, what the name of it is . . . It is er a higher, it's a seat, standing on that, 'e's standing on that . . . this boy is standing on this, seat . . . getting some of this er stuff to . . . biscuit to eat. As he is doing that, the post, it's not a post, it's the, seat, is falling down, is falling over . . .'.

A Sample of E.S.T.'s Incorrect Naming Responses to the Snodgrass and Vanderwart (1980) Pictures

Grapes	eat it and 5 (letters) /græfs/ /grif/ /græs/ . . . /grif/ . . . /gritʃ/ not /græs/ . . .
Lobster	/lɒg/ . . . /lʌb/ . . . /lɒŋ/ . . . Is it l, o ? /lɒ/ . . . /lɒg/ couldn't be a log . . . g . . . /lɒŋ/ . . .
Artichoke	you eat it . . . lettuce, like a lettuce . . . We'll be here till Christmas—not this year, next year (E: 'It's an artichoke') . . . I'm just up to lettuce and then cabbage, not got to blooming artichoke . . . I'm very very pleased I've got round to cabbage!
Strawberry	/sʌmbɛri/ . . . s in it, probably 8 (letters) . . . you get fed up with /sə/ /sʌmbɛri/ . . .
Sledge	no, that's . . . it's cold, I know what it does (E: '/slə/') /slʌg/ /slʌdʒ/ . . . /slain/ . . .
Shoe	foot . . . It's a . . . put on my . . . /ʃɒt/ /ʃut/ . . . foot . . . I should know this . . . 4 (letters) in it, begins with s . . . /sɒl/ . . . shoe, shoes . . . I was crossing in my brain with shop, my shoe, my shop
Balloon	It's a /bærə/ /bælə/ /bælʊʊ/ /blʊʊ/ /blʊʊn/ . . . pipe . . . pipe or a /blʊʊ/ . . .
Skunk	begins with an r . . . /ræbɪn/ . . . something like a rabbit
Axe	3, begins with s, not a saw . . . It's a hammer, it's not a hammer . . . same sort of . . . I jumped at the wrong thing . . . say a lump of wood and you wanted to chop it in two . . . a chopper . . . has it got 3 letters in it? A saw, not a saw . . . (E: '/æ/') /hæm/ (E: '/hæm/'?) Because there's 3 in it . . . /hæn/ . . . /æk/ . . . /æk/ . . . an axe
Record player	It's a . . . It's like a radio . . . It's a . . . um . . . If you want another singing . . . a round disc you put the disc in there . . . rotating . . . I don't know what you actually call it . . . something like a radio, but you get the sounds from the rotating . . . I don't know what you call the plastic stuff (E: '/rə/') /reɪkɔd/ record . . . It's a record something . . . record phonograph . . . /rikɔd/ . . .

Brain (1987), **110**, 631-648

RETINAL VASCULAR ABNORMALITIES IN FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY

A GENERAL ASSOCIATION WITH GENETIC AND THERAPEUTIC IMPLICATIONS

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SUMMARY

Because of occasional reports of exudative retinal detachment with facioscapulohumeral muscular dystrophy (FSH) and deafness, we sought to determine by fluorescein angiography whether there is any general relationship between FSH muscular dystrophy and retinal vascular disease. Peripheral retinal capillary abnormalities, comprising telangiectasis, closure, leakage and microaneurysm formation, were demonstrated by angiography in 56 out of 75 individuals with clinical or genetic evidence of FSH. Only 3 patients had relevant ophthalmoscopic abnormalities of the posterior pole and in only 1 was there consequent visual loss. This study included (1) one FSH family in which the propositus was treated for exudative retinopathy and 13 other subjects had telangiectasis, and (2) 8 cases (including 3 parents of apparently 'sporadic' FSH cases) in which fluorescein angiography confirmed the abnormal genotype, even though clinical examination of skeletal muscle revealed no clear abnormality. There was no correlation between the severity of the muscle disease and the extent of the retinal vascular abnormality. Visual complications of telangiectasis, although rare, may present early in life and before there is overt evidence of muscle disease. Since visual loss may be preventable, ophthalmic examination should be undertaken on infants at risk of having the abnormal gene.

The findings support the hypothesis that retinal capillary abnormalities are an integral part of the FSH muscular dystrophy syndrome and raise the question as to whether analogous capillary abnormalities could be implicated in the pathogenesis of FSH muscle disease.

INTRODUCTION

Patients with facioscapulohumeral muscular dystrophy (FSH) (Duchenne, 1862, 1872; Landouzy, 1874; Landouzy and Dejerine, 1884) may first present because of visual loss (Small, 1968; Taylor *et al.*, 1982; Gurwin *et al.*, 1985). Such a presentation of this autosomal dominant disease is nevertheless distinctly rare, and generally FSH is not thought usually to affect tissues other than skeletal muscle. There have, however, been recent reports of retinal 'Coats' syndrome' in patients with severe FSH and deafness (Small, 1968; Taylor *et al.*, 1982; Wulff *et al.*, 1982). Sensorineural

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deafness has also been reported in patients with early onset severe FSH (Carroll and Brooke, 1979; Meyerson *et al.*, 1984; Korf *et al.*, 1985), and it has been argued that such cases of 'complicated' FSH may constitute a small genetically distinct form of dystrophy. The expression of the FSH gene in skeletal muscle is highly variable (Tyler and Stephens, 1950). Although some patients are severely disabled (Carroll and Brooke, 1979), 'abortive' cases without significant muscle weakness may be virtually as common as symptomatic cases (Walton and Nattrass, 1954); penetrance is not invariably complete (Dubowitz, 1978).

Recently we have seen retinal capillary telangiectasis with FSH and deafness in one family, although only 1 of the 4 subjects had consequent visual loss, due to a macular scar (Gurwin *et al.*, 1985). These observations, together with previous reports (Small, 1968; Taylor *et al.*, 1982; Wulff *et al.*, 1982), might suggest that retinal telangiectasis accompanies a rare subgroup of FSH associated with deafness. On the other hand, they also raise the question as to whether documentation of telangiectasis could help to identify individuals with the FSH gene. Because 'Coats' syndrome' is thought to be of vascular origin, and is potentially treatable, we sought to determine by fluorescein angiography whether any general association exists between retinal vascular disease and FSH.

PATIENTS AND METHODS

Fluorescein angiography was performed on a total of 67 (59 white and 8 Indian) subjects with clinical signs of FSH, as well as 30 of their first degree relatives at risk of having the abnormal gene. These are in addition to the 4 cases previously reported from Moorfields and Hammersmith Hospitals (Gurwin *et al.*, 1985). Details concerning each FSH propositus were obtained from the records of the National Hospital for Nervous Diseases, Queen Square. The diagnosis of FSH in these propositi had been made following clinical examination as well as electromyography and, in all but 2, muscle biopsy to exclude clear evidence of clinically similar disorders such as spinal muscular atrophy (Furukawa *et al.*, 1969), mitochondrial myopathy (Hudgson *et al.*, 1972) and congenital fibre type disproportion (Brooke *et al.*, 1979). Other family members were then traced and examined by one of us (R.B.F.) for typical signs of FSH muscular dystrophy. Three of the 67 patients traced from the National Hospital had clinical hearing loss.

The purpose of the study was explained to the subjects, who were reviewed at Moorfields Eye Hospital. Following direct and indirect ophthalmoscopy, fluorescein angiography was performed using 5 ml of 20% fluorescein sodium. During dye transit special attention was paid to the peripheral retina where evidence of focal nonperfusion or capillary leakage of fluorescein was sought. Angiograms were also performed on 9 definitely unaffected parents or spouses of affected cases. These angiograms were used, together with a series of 80 normal angiograms undertaken in a previous study, to establish features of the normal peripheral retinal vasculature. In the small number of patients where there was doubt as to the presence of abnormality, the angiograms were considered normal. This was a particular problem in the presence of myopia.

RESULTS

Of the 67 angiograms performed on patients with signs of FSH muscle disease, 3 were technically unsatisfactory. Of the remaining 64 subjects, 48 were considered to have abnormal retinal vasculature in at least one eye (figs 3–8); in all 48 (42 white and 6 Indian) cases there were changes in the retinal periphery and in only 3 was the posterior pole ophthalmoscopically abnormal. In its mildest form the abnormality was recognized as a simplification of the retinal vascular bed, the capillaries being longer, wider and fewer in number than normal; these changes, described as 'telangiectasis', were rarely detectable by ophthalmoscopy and were usually limited to the peripheral retina. In more advanced disease there were microaneurysms and areas of capillary closure. The telangiectasis was accompanied by ophthalmoscopically detectable retinal oedema and exudates in the most severe cases and was frequently accompanied by fluorescein leakage from capillaries as detected by angiography. Visual loss due to retinal vascular disease was seen in only 2 cases: Case II.3 (Family A) reported below, and 1 other patient (Gurwin *et al.*, 1985) who had a macular lesion which was considered to be secondary to peripheral retinal telangiectasis. There was no correlation between severity of FSH muscle disease and the extent of the retinal capillary abnormality.

Ten FSH subjects were born before term; only 2 cases are thought to have had birth weights below 2 kg, 1 of whom received high ambient oxygen. Two FSH subjects from the families studied had had an eye removed. In 1, an eye had been enucleated two years before this study because of secondary complications of retinal detachment which were themselves ascribed to the effects of a cricket ball injury seventeen years previously; histopathological examination showed subretinal proteinacious exudate which was thought to be of *recent* origin (Prof. A. Garner). His opposite eye showed retinal telangiectasis. Muscle disease had not been detected at the time of enucleation, but was discovered following the diagnosis of FSH muscular dystrophy in his brother. The second patient (Family B, Case I.1) is detailed below.

Eight of the 30 first degree relatives without clear signs of muscle disease had abnormal angiograms (and are therefore included within the total of 75 individuals considered to have evidence of FSH). These 8 included 2 cases (Case III.5, Family A—fig. 1; Case II.3, Family B—figs 2,6) in whom the FSH genotype was implied by the family pedigree, and 3 parents of the apparently isolated cases of FSH mentioned below. Three other cases (aged 11, 15 and 21 yrs) were at an age when muscle signs may not have developed, but genetic advice may be sought.

In 9 families, 3 or more affected relatives were studied; in 4 of these families all affected members had demonstrable retinal vascular disease, in 5 both normal and abnormal angiograms were recorded and in none did every member have normal angiography.

Four cases without family history of muscle disease were seen whose parents were examined and concluded to have normal musculature. These four cases are as follows. (1) One 17-yr-old patient with sensorineural deafness and retinal telangiectasis with leakage. His father had telangiectasis with peripheral scarring, but the clinical significance of his thin tibialis anterior muscles had been considered dubious. The patient's mother's angiogram was normal. (2) A 12-yr-old boy with widespread telangiectasis. His father has telangiectasis and his paternal grandmother had a severe lordosis from the age of 40 yrs but has a normal fluorescein angiogram. The mother's angiogram was not adequate for assessment. (3) A 14-yr-old boy with predominantly scapuloperoneal weakness. His mother had telangiectasis with peripheral closure. His father's angiogram was within normal limits for myopic eyes. (4) A 20-yr-old man. Neither the patient nor either of his parents had conclusive capillary abnormalities on angiography.

Family Studies

The FSH muscular dystrophy cases studied included members of 2 large families (figs 1,2; Table) which are presented by way of illustration. The muscle disease in this subset of patients did not differ clinically from that in the group as a whole. In both pedigrees the autosomal dominant nature of the disorder was apparent on initial questioning of the propositus, which is in contrast to some other families in which no affected relatives were known, or were only found after prolonged enquiry. It is possible that the more constant expressivity in these families implies a disorder different from that in other cases but it seems more likely that the variation was purely a chance occurrence.

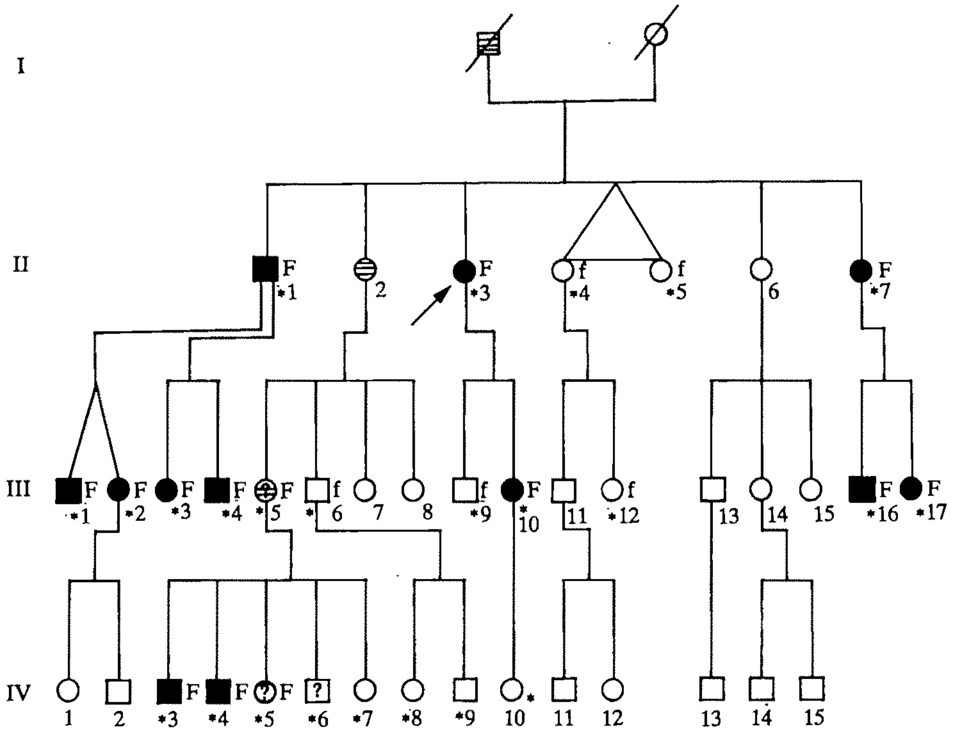


FIG. 1. Pedigree, *Family A*. Asterisks identify individuals examined. Full shading denotes examined cases with clinical signs of muscle disease. Horizontal hatching = implied FSH genotype; vertical hatching = cases affected by history; ? = muscle signs of equivocal significance; F = abnormal fluorescein angiogram; f = normal fluorescein angiogram.

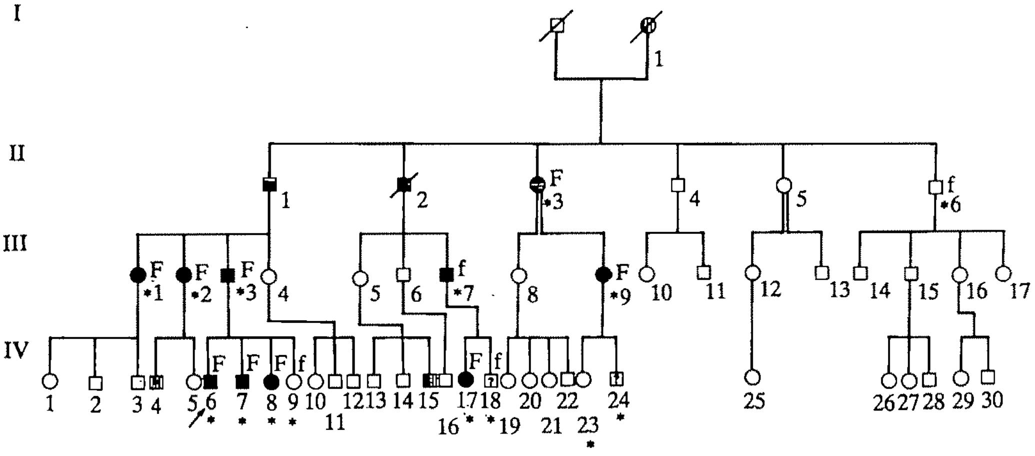


FIG. 2. Pedigree, *Family B*. Symbols as for fig. 1. Generation V not shown.

TABLE. SUMMARY OF FINDINGS ON OPHTHALMOSCOPY AND FLUORESCEIN ANGIOGRAPHY IN 14 CASES FROM FAMILY DEPICTED IN FIG. 1

	Sex,	*FSH muscle*	*Fundus changes*[e]	
Case	*age (yrs)*	*condition*[d]	*Right eye*	*Left eye*
II.3	F 58	Severe	TCL (focal)	TCL (diffuse) haemorrhages, exudates
II.1	M 62	Moderate	TCL (focal)	TC (focal)
II.7	F 49	Moderate	TCL (focal)	TCL (focal)
III.1[a]	M 29	Severe	T (focal)	T (focal)
III.2[b]	F 29	Moderate	TCL (diffuse)	T (focal)
III.3[c]	F 14	Trivial	TC (focal)	T (focal)
III.4	M 12	Trivial	TCL (diffuse) haemorrhages, exudates	TCL (focal)
III.5	F 38	Equivocal	TC (focal)	T (focal)
III.10	F 29	Moderate	T (focal)	N
III.16	M 22	Trivial	TC (focal)	TC (focal)
III.17	F 20	Mild	TCL (diffuse)	TCL (diffuse)
IV.3	M 15	Trivial	TC (focal)	T (focal)
IV.4	M 13	Trivial	TC (focal)	N
IV.5	F 11	Equivocal	TC (focal)	T (focal)

[a] Preterm delivery, birth weight 2.8 kg. [b] Preterm delivery, birth weight 2.3 kg. [c] Preterm delivery, birth weight 2.5 kg. [d] Trivial = patient unaware of muscle abnormality, but abnormalities detected on examination; mild = no disability; moderate = disability present; severe = uses aids to walk or has required surgery. [e] T = telangiectasis; C = capillary closure; L = leakage; N = no abnormality.

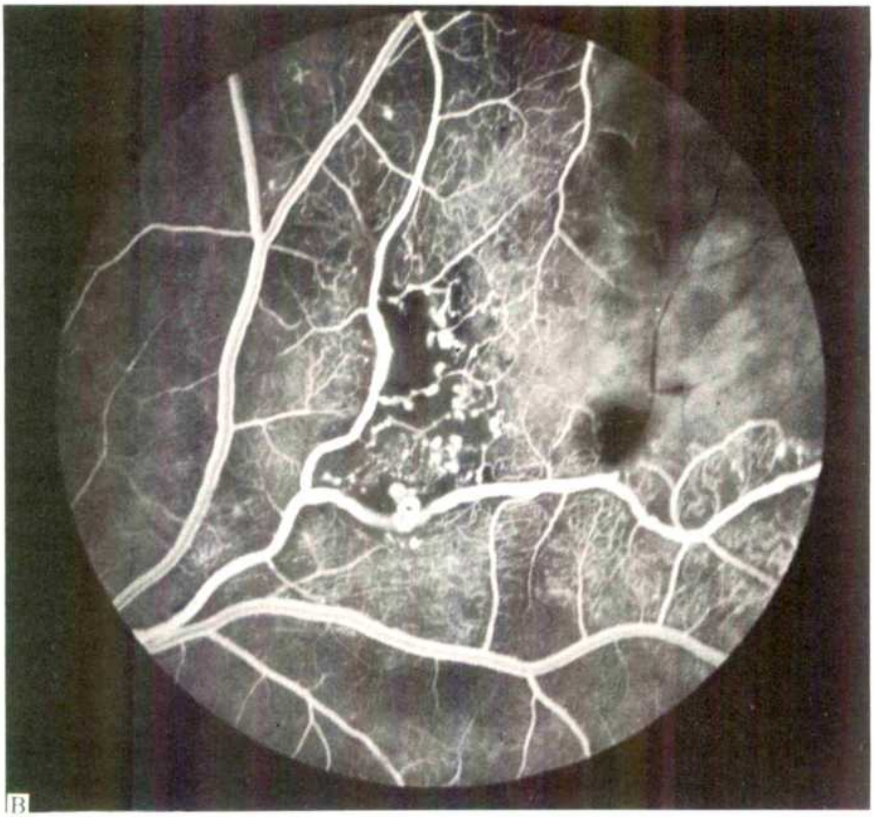


FIG. 3. *Family A, Case II.3.* A, (*see* colour plate) colour photograph of left fundus demonstrating retinal oedema and exudate above macula, surrounding haemorrhage and tortuous telangiectatic vessels. B, fluorescein angiogram demonstrating telangiectasis and capillary closure and dye leakage into the retina.

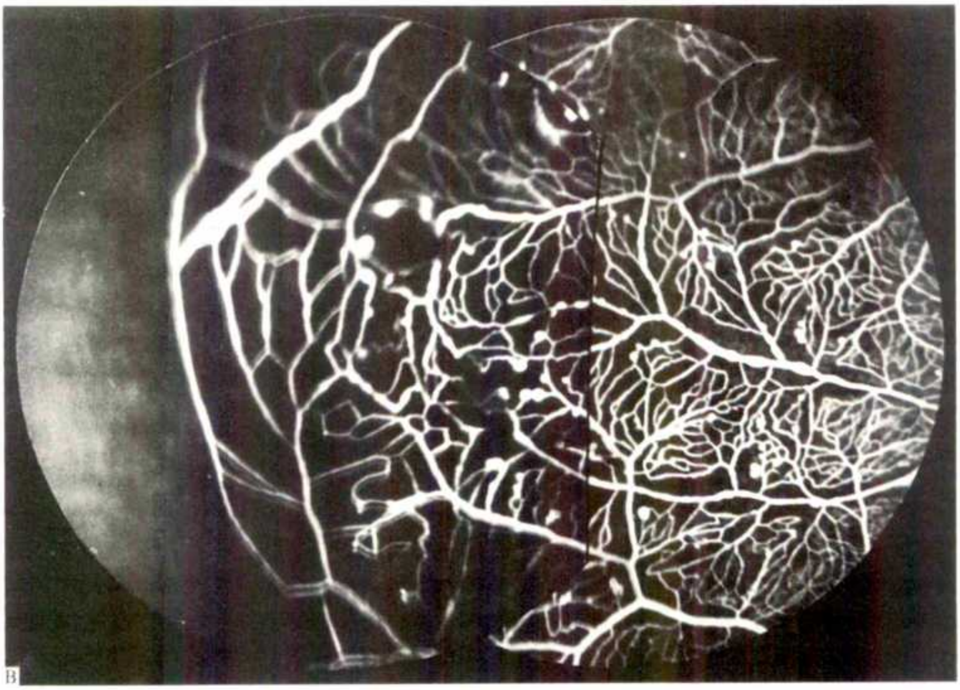


FIG. 4. *Family A.* A, *Case III.4.* Colour photograph of temporal retina demonstrating telangiectasis, haemorrhages and scattered exudates (*see* colour plate). B, angiography confirming the vascular changes, comprising dilated vascular channels, microaneurysms and peripheral closure.

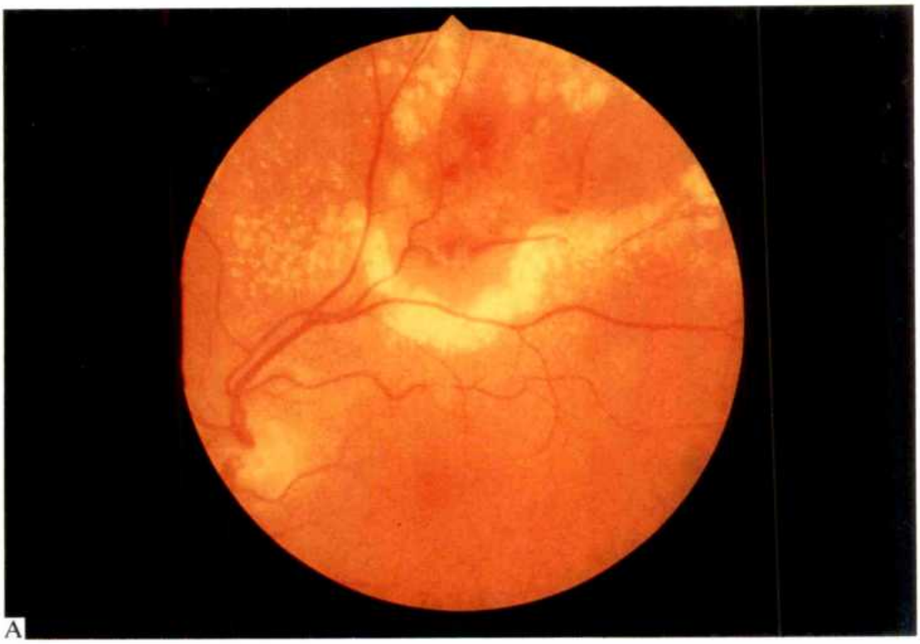


FIG. 3A

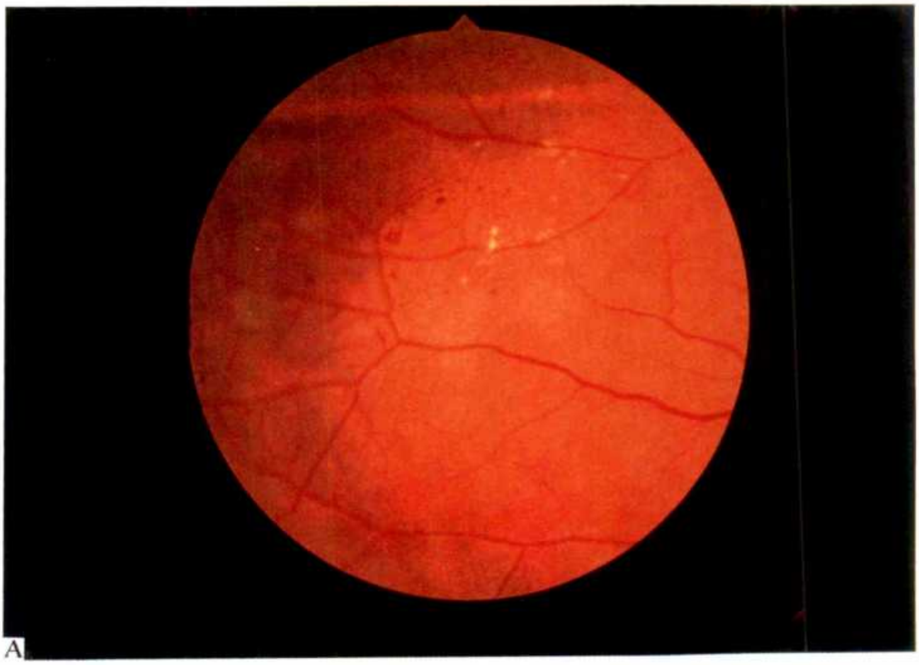


FIG. 4A

PLATE II

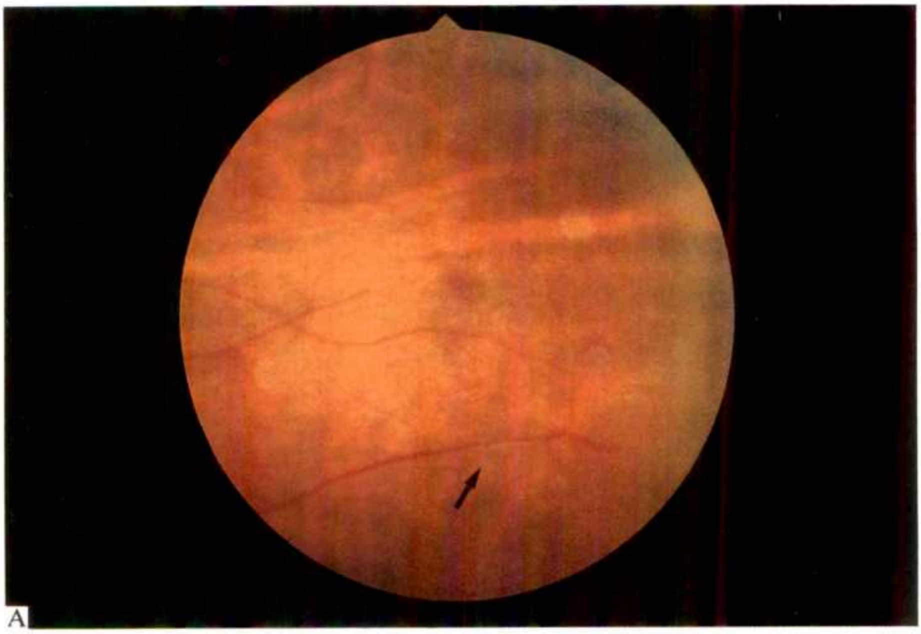


FIG. 7A

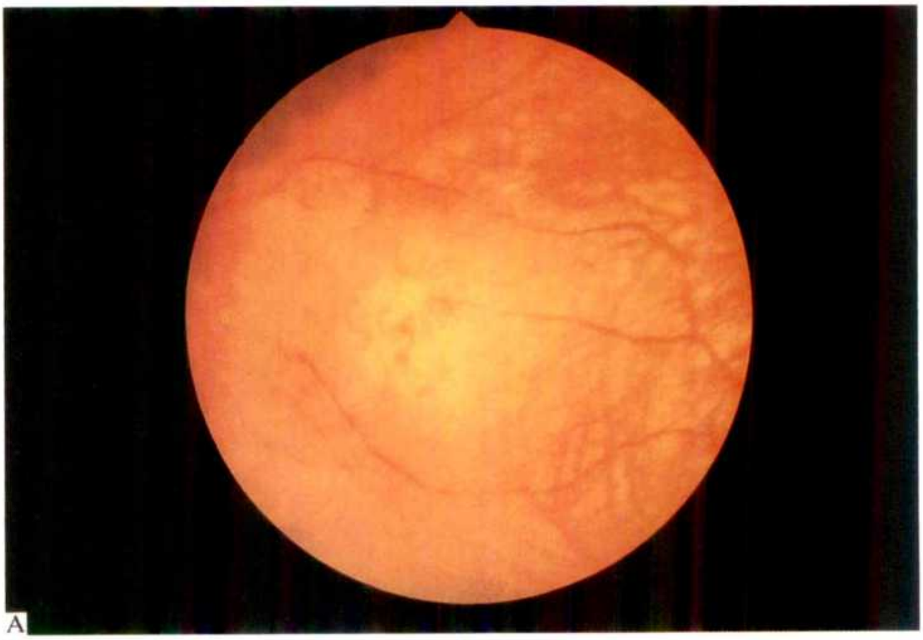


FIG. 8A

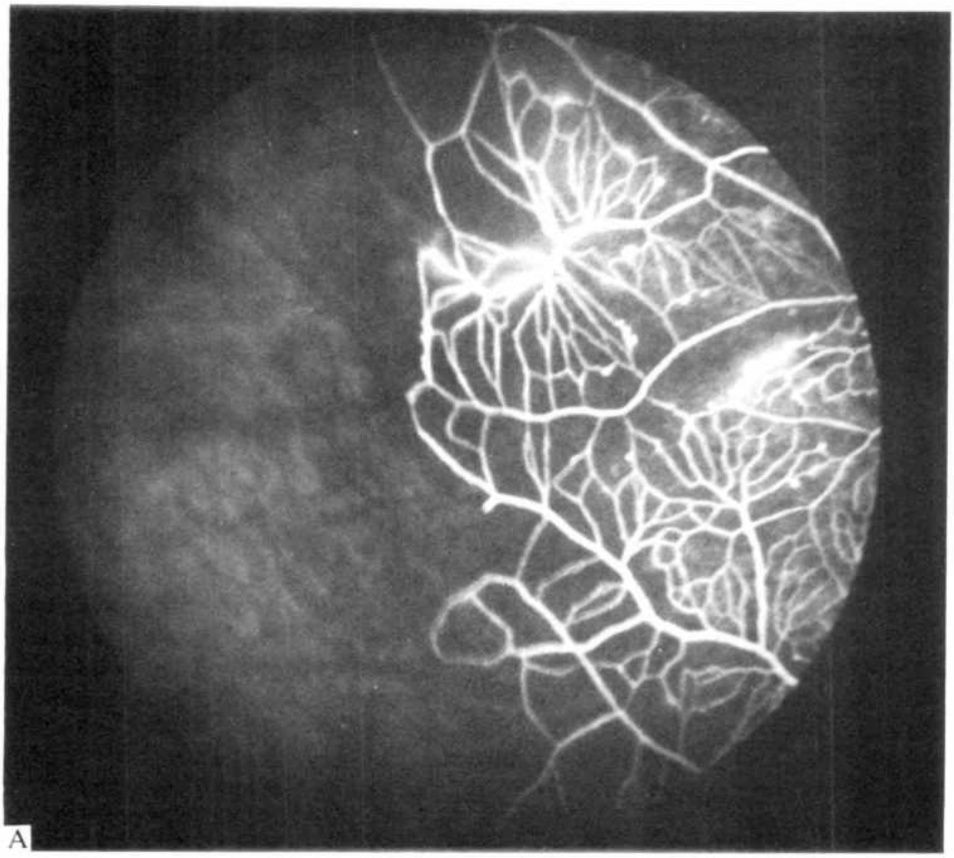


FIG. 5. *Family A*. A, *Case III.17*. Fluorescein angiogram of temporal periphery of right eye demonstrating microaneurysms, capillary telangiectasis and closure. B, *Case III.2* (see overleaf). Angiogram of the right eye periphery showing marked vascular changes in the lower part of the frame and more subtle changes above.

Family A (*fig. 1; Table*). The propositus (Case II.3), aged 58 yrs, had noticed deteriorating vision for several months before the commencement of our study. A diagnosis of a 'Coats'-like' lesion had, however, been made several years previously, although no treatment had then been instituted because acuity was unaffected. At the time of our initial examination left visual acuity was 6/9; there were exudates in the superotemporal retina of the left eye and macular oedema, and fluorescein angiography revealed extensive retinal telangiectasis (fig. 3). Visual acuity with the right eye was 6/5 and telangiectasis was present in the peripheral fundus. She was not hypertensive or diabetic. Argon laser photocoagulation has been applied to the left eye on three occasions. During therapy visual acuity fell to 6/18, but has subsequently recovered following resolution of oedema and exudates, and has remained stable at 6/9 for nine months. Angiography was performed on 19 relatives of Case II.3, of whom 12 had clinical evidence of FSH muscle disease; 1 subject

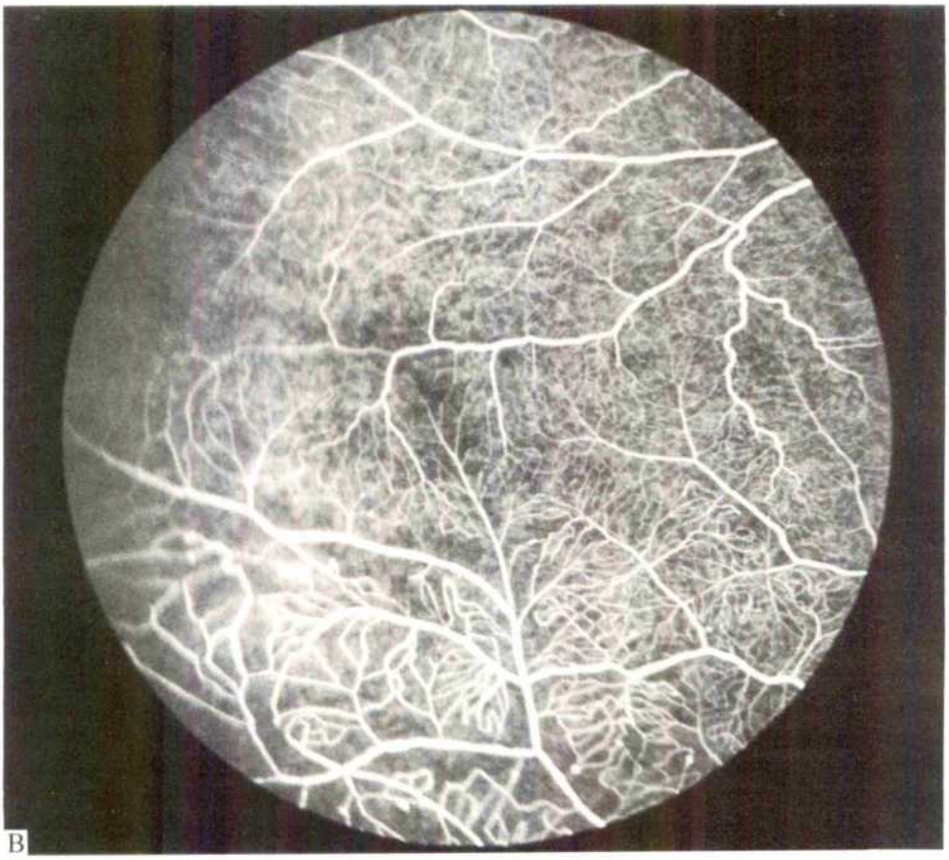


FIG. 5B.

(Case III.5), who was thinly built, had telangiectasis but no unequivocal signs of muscle disease although 2 of her sons had scapular winging and 2 other children had questionably abnormal shoulder contours (Table, fig. 1). Peripheral vascular abnormalities including telangiectasis and capillary closure were identified in the 12 clinically affected subjects but not in those normal relatives indicated in fig. 1. Not one of these cases is clinically deaf. The lack of correlation between the severity of the muscle disease in this family and the extent of the retinal disease is illustrated by Case III.17 who has trivial FSH muscular dystrophy and widespread peripheral retinal telangiectasis (fig. 5), whereas her cousin, Case III.1, has more severe FSH, but more restricted telangiectasis. In Case III.3 the evidence for muscle disease and retinal abnormalities was slight in both cases.

Family B (*fig. 2*). Only 2 members of this family (Cases IV.6, seen at age 29 yrs, and III.7, age 44 yrs) have significant symptomatic muscle disease, although other family members (IV.4, II.2, IV.15 and I.1) are known to have had family characteristics such as protruding shoulderblades or inability to play wind

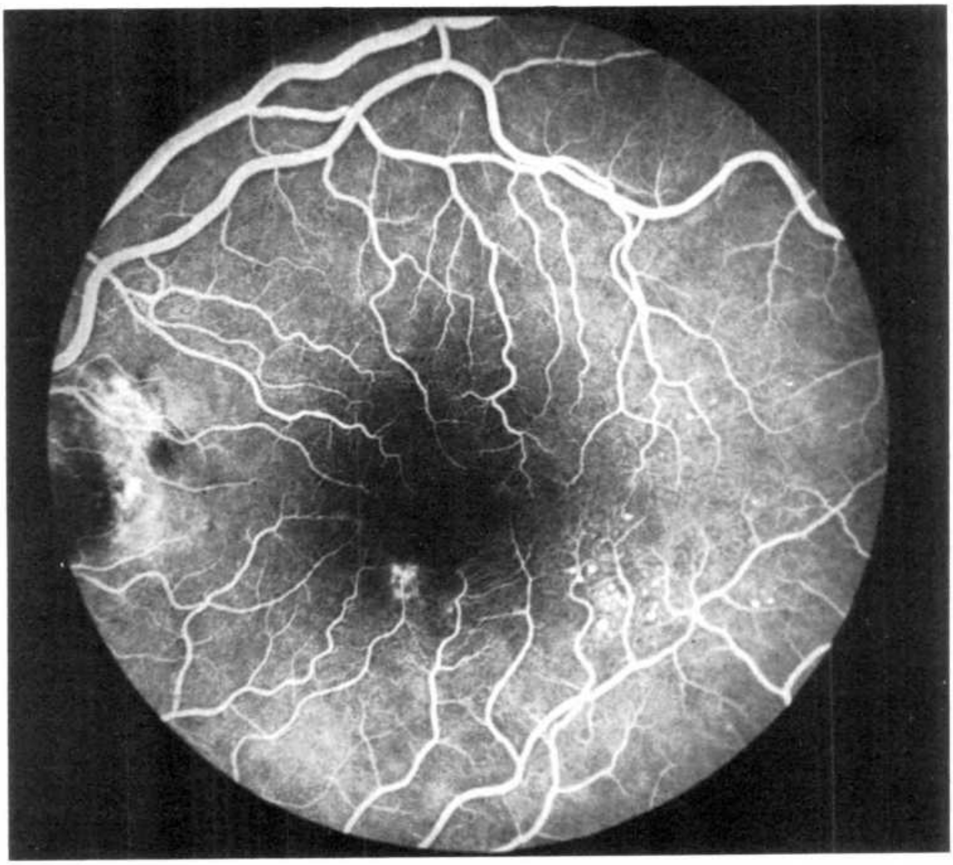


FIG. 6. *Family B, Case II.3.* Fluorescein angiogram of the left eye showing microaneurysms around the fovea and leakage of dye into the retina. A fine linear exudate was also visible ophthalmoscopically.

instruments. Again, there was no correlation between severity of eye and muscle manifestations. Thus Case III.7 (who has moderately severe muscle disease) did not have capillary abnormality evident on angiography, although his daughter (Case IV.17; age 19 yrs), whose only detectable muscle abnormality is minor facial weakness, has a sheathed vessel at the temporal periphery of the left retina, with marked associated capillary telangiectasis, closure and slow blood flow (fig. 7).

Case II.3 (aged 71 yrs) has no definite evidence of muscle disease; her thin shoulder girdle musculature was considered normal for her age. However, ophthalmoscopy revealed parafoveal exudates and haemorrhages; fluorescein angiography demonstrated associated telangiectasis, leakage and microaneurysms (fig. 6), as well as peripheral telangiectasis. She is not diabetic or hypertensive. Her daughter has minor signs of FSH and telangiectasis. Case I.1 (born 1885), who had protruding shoulderblades and was myopic, suffered severe bilateral visual loss as a

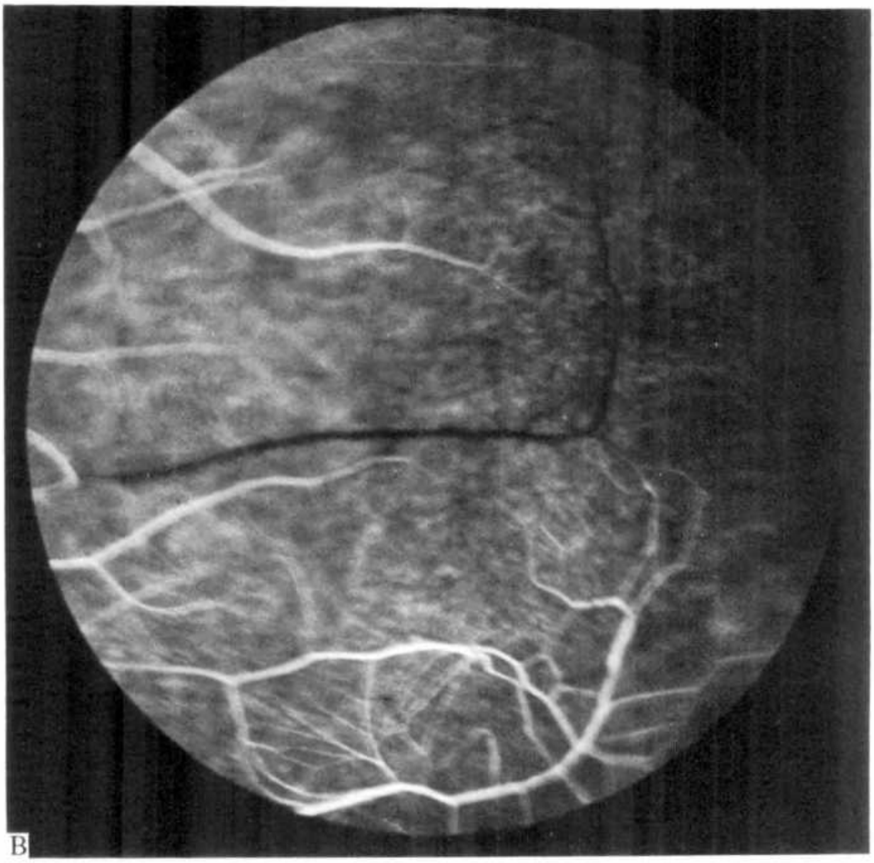
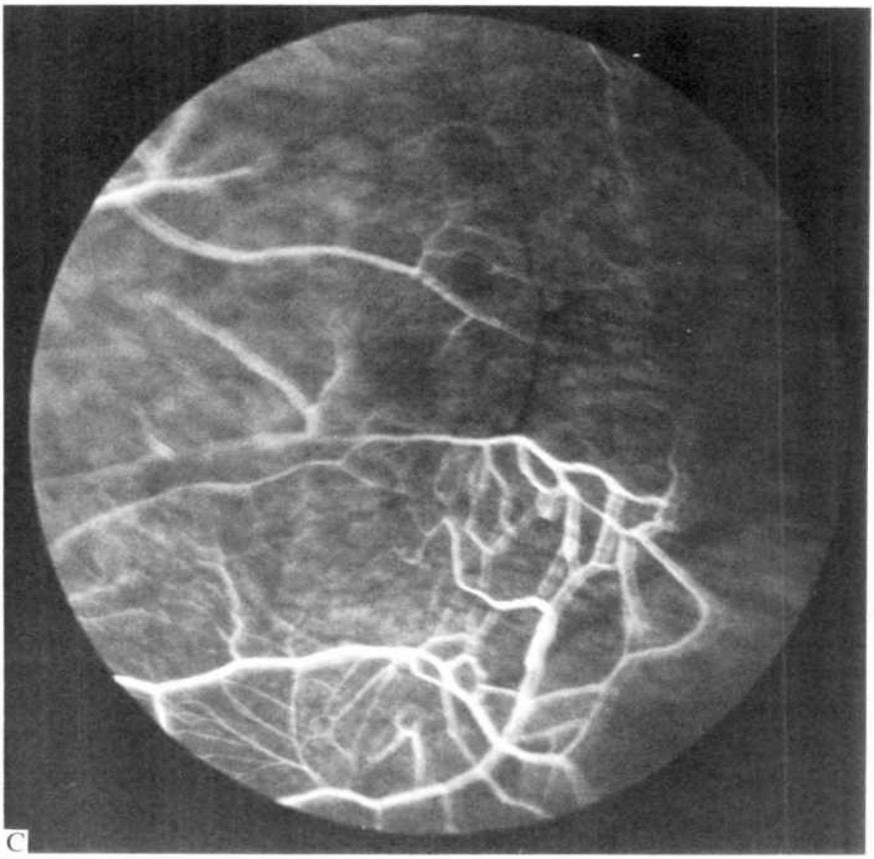


FIG. 7. *Family B. Case IV.17.* A, (*see* colour plate) colour photograph of the left eye peripheral fundus illustrating a sheathed vein (arrow). B–D, serial fluorescein angiograms showing slow filling of the vein and vascular closure (C, D opposite).

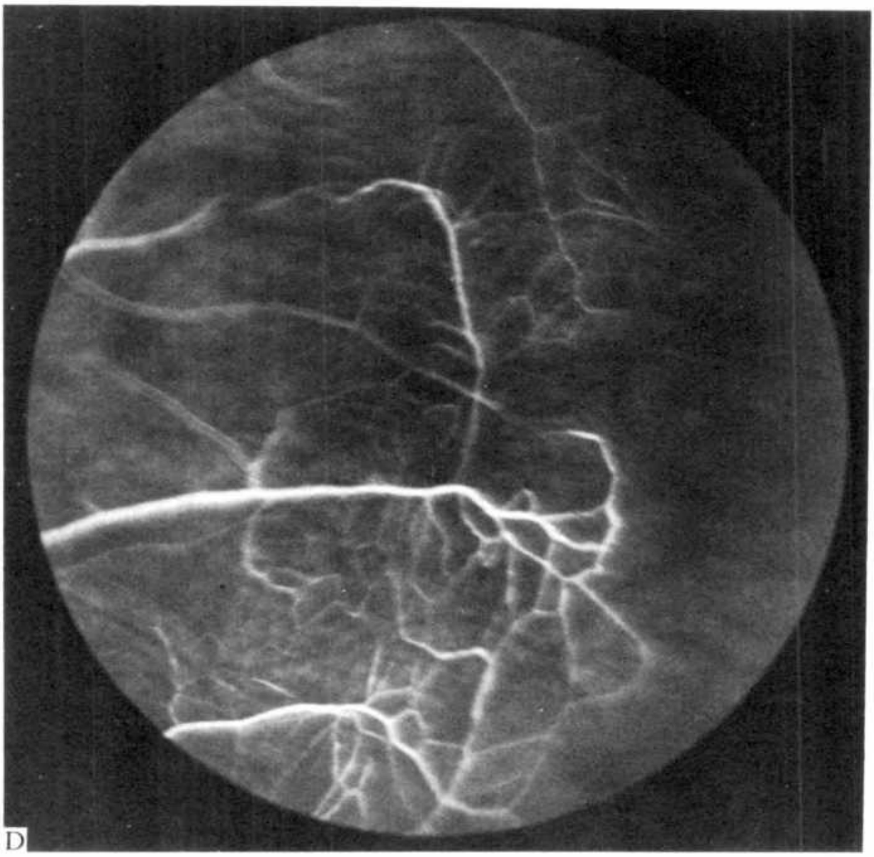
teenager. One eye, enucleated at the Western Ophthalmic Hospital in 1948, was reported to show 'retinal detachment, subretinal haemorrhage and glaucoma'.

DISCUSSION

Retinal telangiectasis was found to be extremely common in FSH muscular dystrophy, and appears to be an integral part of that genetic disorder; it is not restricted to patients with FSH and deafness. The occasional occurrence of massive exudative retinal detachment (referred to as Coats' syndrome) (Taylor *et al.*, 1982; Wulff *et al.*, 1982) in FSH muscular dystrophy is clearly not a chance association, but rather a severe but rare manifestation of retinal capillary leakage and telangiectasis. Retinal vessel changes were not detected in some FSH muscular dystrophy patients. It is not possible, however, to exclude vascular disease in these cases, because the entire periphery of each eye cannot be photographed during the brief period of initial dye transit.



C



D

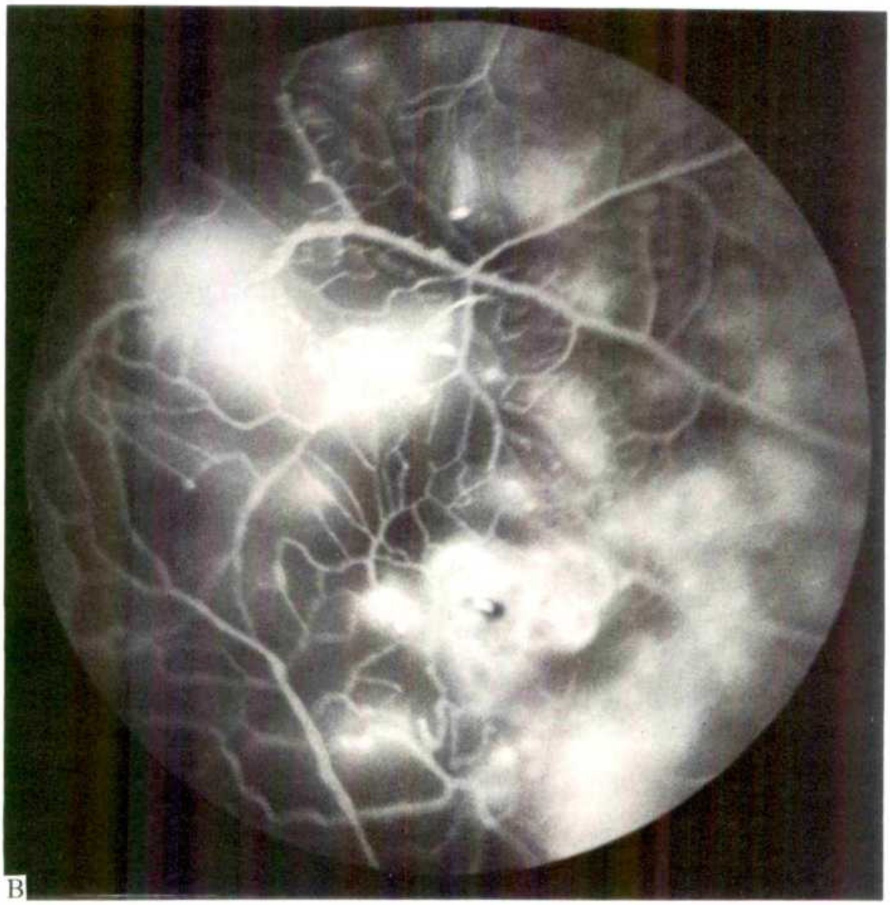


FIG. 8. A, (*see* colour plate) colour photograph of temporal retina of an 18-year-old girl with moderate FSH showing marked telangiectasis, retinal oedema and exudates. B, fluorescein angiography of this eye illustrating more widespread vascular changes and dye leakage.

The presence of retinal vascular changes in such large numbers of FSH subjects could not be due to the presence of unrelated disease. A small number of our patients were born prematurely; those detailed in the Table were unlikely to have developed retinopathy of prematurity because they had high birth weights and did not receive high ambient oxygen after birth. Familial telangiectasis has been described in dominant exudative vitreoretinopathy (Ober *et al.*, 1980). The characteristic abnormality in both retinopathy of prematurity and dominant exudative vitreoretinopathy is the radial arrangement of telangiectatic capillaries with terminal fluorescein leakage on angiography; such changes were not seen in any of the patients described here. It is well recognized that retinal vascular disease is present in a variety of generalized disorders such as diabetes mellitus, sickle haemoglobinopathy and uncontrolled hypertension, as a consequence of local vascular obstruction or in response to irradiation. Our results cannot be explained by the presence of such precipitating factors, and the distribution of vessel disease was unlike that seen in these disorders. The retinal capillary bed becomes simplified in old age (Cogan, 1963), but only 4 of our patients with retinal capillary abnormalities were aged over 60 years.

Curiously, this association between FSH muscular dystrophy and retinal telangiectasis has not previously been suspected. This may reflect the difficulty of each specialist in recognizing subtle signs proper to the province of the other; few neurologists examine the retinal periphery by indirect ophthalmoscopy and few ophthalmologists are skilled in detecting minor degrees of skeletal muscle wasting. In this study, relevant ophthalmoscopic retinal posterior pole abnormalities were present in only 3 patients, and in neither of the 2 patients who had eye enucleation was the muscle disease detected by the ophthalmologist.

The presence of blood vessel changes in the retina has important implications for FSH muscular dystrophy, both with respect to the pathogenesis of the muscle disease and from the clinical standpoint.

Coats' Disease: a Disorder of Retinal Capillaries

'Coats' disease' implies exudative retinal detachment associated with retinal vascular changes. As originally described (Coats, 1908) and later defined (Manschot and de Bruijn, 1967), this condition is typically unilateral, not inherited, and is predominantly an affliction of young boys. If diagnosed early it may be successfully treated by photocoagulation (Campbell, 1976; Theodossiadis, 1979; Ridley *et al.*, 1982). Changes in the peripheral retinal vasculature are important in the pathogenesis of the detachment (Campbell, 1976). The primary defect may be congenital and is now thought to be within the peripheral retinal capillary endothelium (Tripathi and Ashton, 1971), in which abnormal permeability results in secondary phenomena such as microaneurysm formation, capillary closure or dilatation, and leakage of plasma constituents into the retina (manifest clinically as oedema with surrounding exudate), serous retinal detachment, scarring, neovascularization, and glaucoma. Posterior pole abnormalities such as disciform scars (Coats, 1908; Gurwin *et al.*, 1985) may result from accumulation of exudates at the fovea. Terms such as 'Coats' syndrome' and 'Coats' lesions' have been used by some authors to describe similar retinal disease which does not conform to Coats's original description; for example, if the disease is bilateral (Green, 1967; Campbell, 1976), familial (Campbell, 1976), occurs in adult life (Henkind and Morgan, 1966) or is associated with other eye disease (Morgan and Crawford, 1968). To avoid confusion such conditions are now often designated 'retinal telangiectasis with detachment'.

Muscle Pathology in FSH: Is There a Capillary Abnormality?

If capillary abnormalities are important in the pathogenesis of retinal disease in FSH, might there be an analogous capillary abnormality in skeletal muscle (or cochlea) affected by FSH? Perivascular inflammation has been described as a prominent feature in FSH muscle (Munsat *et al.*, 1972) even though adjacent areas of muscle appear almost normal or else nonspecifically dystrophic. Small angular fibres are sometimes present without any collateral evidence of neurogenic disease; such fibres are, however, also seen in vascular muscular disorders. These findings in muscle would be consistent with a patchy vasculopathy, or plasma leakage, but there have been no extensive studies of vascular ultrastructure in FSH muscle. The pathogenetic relationship between the telangiectatic syndrome we describe, 'Coats' disease' as traditionally defined and the muscle disease in FSH muscular dystrophy is not known. Although blood vessel abnormalities may occur as a secondary response in diseased retina (Morgan and Crawford, 1968) and skeletal muscle (Jerusalem *et al.*, 1974), it is possible that there is a primary endothelial abnormality both in Coats' disease and in FSH muscular dystrophy. The vascular lesions of the retina and muscle may have a common pathogenesis and give a clue as to the aetiology of the FSH muscular dystrophy. The question also arises as to whether or not the peculiarly selective involvement of muscles in FSH might be related to idiosyncratic variations in the architecture of the microvasculature of different muscles (Blomfield, 1945) and/or to the pattern of their embryological development. Further studies of the structure and function of vasculature in FSH muscle are clearly needed.

Visual Loss in FSH: a Preventable Complication

Whereas retinal vascular disease appears to affect the majority of patients with FSH, the results of this survey and the previous literature imply that visual loss is uncommon. The importance of the observation lies in the fact that vascular disease is potentially treatable if identified early. There are cases of FSH in which ocular lesions resulted in scars (Gurwin *et al.*, 1985) or exudative detachment (Taylor *et al.*, 1982) in early childhood and which were too advanced for treatment by the time of diagnosis. These observations imply that indirect ophthalmoscopy should be performed on infants at genetic risk of FSH muscular dystrophy in order to exclude the presence of treatable retinal vascular disease.

Genetic Questions

The demonstration of a retinal vascular abnormality may be important for genetic counselling. The abnormal genotype for FSH muscular dystrophy may be difficult (Walton, 1955) or impossible (Dubowitz, 1978) to detect on clinical examination of muscles. In Family A presented here, there were cases (notably III.4 and III.17) in which the retinal telangiectasis was more readily apparent than the muscle disorder. If there is doubt as to the presence or absence of FSH muscular dystrophy in a family member fluorescein angiography could be used to detect the presence of the abnormal genotype, although evidence of retinal abnormality, like that of muscle disease, may not invariably be clear-cut. There is little doubt that the retinal changes may be so mild that it would be unjustified to make the genetic diagnosis on the basis of the fundus findings alone.

Finally, detection of retinal vascular disease may help distinguish FSH muscular dystrophy from some other forms of neuromuscular disease such as spinal muscular atrophy (Furukawa *et al.*, 1969), mitochondrial myopathy (Hudgson *et al.*, 1972), congenital fibre type disproportion (Brooke *et al.*, 1979) and, especially, polymyositis, which may be clinically (Rothstein *et al.*, 1971) and pathologically (Munsat *et al.*, 1972) indistinguishable from FSH.

General Comments on FSH

It was not intended that this investigation should have been an epidemiological survey. Nevertheless the study of such a large number of FSH cases and their family members has inevitably resulted in deductions concerning FSH which might not readily be apparent in smaller studies. First, there is the question of the prevalence of the FSH gene. This has been quoted as between 2 per million (Morton and Chung, 1959) and 62 per million (Becker, 1964). The fact that our 75 genetically affected subjects are derived from a population of no more than 20 million, together with the knowledge that there are many FSH individuals in this region whom we have not seen, means that the former estimate cannot possibly apply in the south of England; even the latter figure may be an underestimate. Incomplete ascertainment of people with the abnormal gene in previous studies might have been due to the large number of cases in whom the condition is not sufficiently obvious for affected individuals to seek medical advice. The existence of such cases was emphasized by Landouzy and Dejerine (1884) and by Walton (1955), and is particularly well illustrated in Family B, in which only 2 cases (once removed first cousins of each other) are symptomatic.

From this it follows that a substantial number of symptomatic cases must be the offspring of trivially affected parents. Carroll and Brooke (1979) noted that 6 of 11 of their young patients with severe FSH had deafness and asymptomatic parents; a further 6 such young deaf patients were reported by Korf *et al.* (1985). Their arguments that FSH with such variable expressivity and deafness represents a genetically distinct entity is not supported by this study since a very large number of FSH patients who are not deaf also have asymptomatic parents.

A number of adolescent patients and their parents firmly maintained that the onset of the muscle symptoms and also the loss of bulk of the shoulder girdle muscles had been very rapid; in 1 patient this was precipitated by influenza. Such a time course is more characteristic of myositis than of dystrophy, yet was initially described by Duchenne (1862) whose patient (his fig. 16) had dominant disease and long-standing facial weakness. Until the age of 12 years the disease appeared stationary; at that age upper arm and shoulder weakness appeared and progressed so rapidly that within three months the shoulder girdle muscles were in effect destroyed. Arrested progression of FSH is also well documented (Duchenne, 1872; Landouzy and Dejerine, 1884; Carroll, 1979; Kakulas and Adams, 1985). The variable expression of the FSH gene might be related to these unpredictable episodes of rapid progression—'sa marche capricieuse et irrégulière' (Duchenne, 1862; his fig. 2)—the immediate causes of which have yet to be identified.

There was also significant intrafamilial variation in the distribution of muscle weakness. Predominantly scapulohumeral or scapuloperoneal involvement was seen in individuals whose relations were clearly affected by FSH dystrophy. This is in line with the observations of Pearson (1933), and of Duchenne (1872) who described scapulohumeral disease without facial weakness in a patient (M.X.) whose 2 children exhibited early and marked facial weakness. Such atypical cases may lead to diagnostic uncertainty. The question of whether or not an autosomal dominant dystrophy, which is consistently scapuloperoneal in distribution (Thomas *et al.*, 1975), is a genetically distinct entity is not yet answered. Since retinal vascular changes were seen in all the larger families studied, the presence or absence of such changes did not provide evidence for the existence of more than one genetic disorder within this group.

The presence of large numbers of patients with trivial disease calls into question the appropriateness of the term 'muscular dystrophy' which is traditionally used for those inherited diseases of muscle which are severe, progressive, and in most cases were described before 1900. In contrast, the term 'myopathy' is now used for more recently defined and relatively benign genetic disorders such as centronuclear myopathy, nemaline myopathy and central core disease. The present study confirms what is apparent from the accumulated literature, namely that although debility undoubtedly does occur in FSH (as it does, for example, within the clinical spectra of nemaline myopathy and centronuclear myopathy), the great majority of persons genetically affected by FSH, even those with symptomatic disease, never become seriously disabled; yet the term 'muscular dystrophy' frequently imparts catastrophic implications to such individuals. Might not 'FSH myopathy' be a more appropriate label for this disease?

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PATHOLOGICAL EYE-HEAD COORDINATION IN ROLL: TONIC OCULAR TILT REACTION IN MESENCEPHALIC AND MEDULLARY LESIONS

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SUMMARY

The fundamental pattern of coordinated eye-head roll motion is based upon utricular/saccular as well as vertical canal input, and mediated by the graviceptive pathways from the labyrinths via pontomedullary vestibular nuclei to the rostral midbrain tegmentum. The tonic bilateral graviceptive input stabilizes the eyes and head in the normal upright position. A unilateral lesion causes imbalance in vestibular tone in the roll plane which results in a tonic ipsiversive ocular tilt reaction (OTR).

OTR, the triad of ipsilateral head tilt, skew deviation and ocular torsion, occurred as a tonic response (nonparoxysmal) persisting over months to years and was presumed to be due to upper brainstem lesions in 3 patients. Precise localization was limited because of the nature of the lesions. A *reversible* tonic OTR was seen with acute infarction of the dorsolateral medulla oblongata in 4 out of 11 patients. It may be explained by an ipsilateral lesion of the posterior canal pathways. Transient OTR seems not to be rare in acute Wallenberg's syndrome and ocular torsion in these patients is dysconjugate with predominant excyclotropia of the ipsilateral hypotropic eye. A deviation of the subjective visual vertical in the direction of the spontaneous head tilt—a previously undescribed feature of OTR—was present in all 7 patients and indicates a pathological shift of the internal representation of the gravitational vector. With respect to perception (subjective vertical) it is proposed that the manifest ipsiversive OTR represents a motor compensation of an apparent eye-head tilt contraversive to the lesioned side. Despite the resulting postural imbalance and the conflicting true vertical of the visual surround, the eyes, head and body are continuously adjusted to what the central nervous system erroneously computes as being vertical.

INTRODUCTION

The ocular tilt reaction is an oculocephalic response consisting of ipsilateral head tilt, skew deviation, and ocular torsion. It was first clearly delineated by Westheimer and Blair (1975*a*, *b*) during electrical stimulation of the rostral midbrain tegmentum in the region of the interstitial nucleus of Cajal of the monkey. Since then only 3 human cases have been reported. A paroxysmal ocular tilt reaction was reported by Rabinovitch *et al.* (1977) in a patient with multiple sclerosis and

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in a patient with a brainstem abscess in the region of the zona incerta by Hedges and Hoyt (1982). Halmagyi *et al.* (1979) documented a reversible tonic ocular tilt reaction in a patient with a partial iatrogenic lesion of the utricle following stapedectomy.

We describe for the first time a *tonic* ocular tilt reaction due to upper brainstem-midbrain lesions in 3 patients and, in 4 others, in relation to lateral medullary lesions (Wallenberg's syndrome). A deviation of the subjective visual vertical towards head tilt, a previously undescribed feature of the condition of ocular tilt reaction (OTR), was present in each of our patients and is, we speculate, secondary to a deviation of the internal representation of the gravitational vector. OTR is best attributed to 'motor compensation' of an apparent eye-head tilt (roll) opposite in direction to the manifest deviation. It probably represents an imbalance in graviceptive vestibular tone in the roll plane due to a unilateral lesion.

PATIENTS AND METHODS

All of 7 patients had acquired ocular motor disturbances with visible vertical separation of the ocular axes and consistent vertical diplopia. We photographed the eyes in multiple positions of gaze, and also the head and trunk; these and medical histories were used to eliminate confusion with congenital vertical strabismus (fig. 1).

The following ophthalmological parameters were determined. (1) Head tilt relative to true vertical in degrees. Most patients exhibited a minor ipsiversive trunk tilt, the angle of which was not measured. (2) Vertical divergence of the two eyes (skew deviation) in degrees with the head upright. Usually it is continuously present with some variation of the amount of divergence due to changes in direction of gaze. In our cases skew deviation appeared to be caused by hypertropia of the contralateral eye while the ipsilateral eye appeared to maintain a normal horizontal position. It could be argued, however, that one eye should assume the primary position of gaze in order to provide fixation without abnormal head position in the fore-aft plane. (3) Cyclodeviation (ocular torsion) in degrees was measured by evaluation of fundus photographs taken with the head upright.

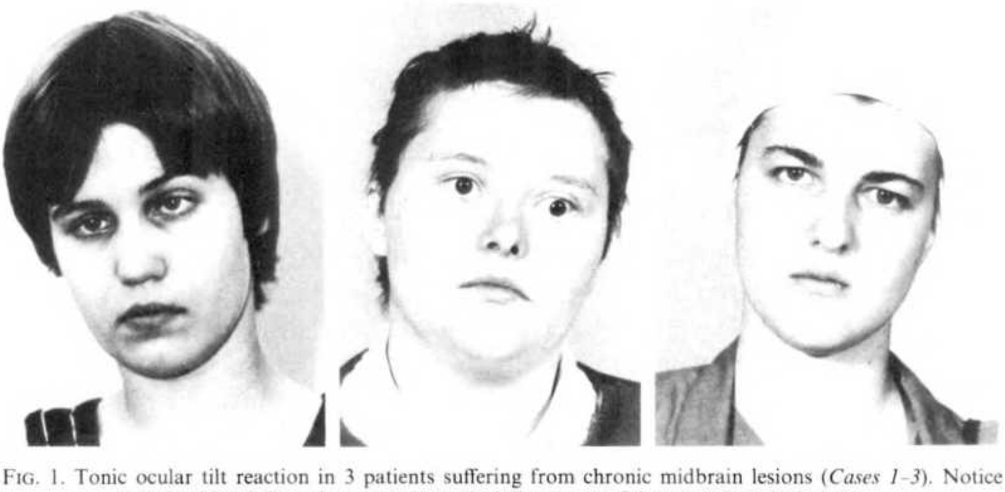

FIG. 1. Tonic ocular tilt reaction in 3 patients suffering from chronic midbrain lesions (*Cases 1–3*). Notice sustained head tilt and concurrent vertical divergence of the eyes (skew deviation).

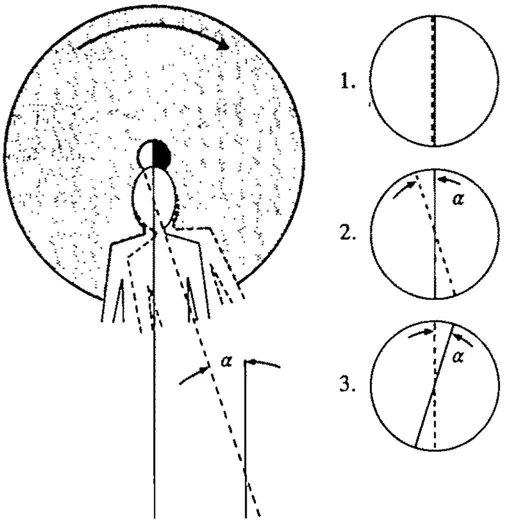

FIG. 2. Determination of the dynamic subjective visual vertical displacement of perceived vertical during rollvection induced by a large hemispherical dome rotating around subject's line of sight. Clockwise rotation causes apparent counter-clockwise tilt of the observer's body (dashed line). The vertical edge (1) separating black and white halves of the test target appears similarly tilted. (2) The perceived tilt is measured by having the subject adjust a test-edge parallel to his apparent vertical (3) dynamic visual vertical.

Measurements of the Visual Vertical

It was the consistent 10 to 15 deg inclination of personal photographs taken by one patient (Case 1) as well as the slope of the writing on a blackboard when she was blindfolded that led us to investigate the subjective vertical more thoroughly in these patients. The subjective static and dynamic visual verticals were measured in all patients. Ten healthy subjects (5 female, 5 male, aged 22–57 yrs) served as controls in the experiments to determine the physiological static and dynamic visual vertical. Each subject sat with his head fixed in the upright position by means of a bite board or a band fastened around the occiput, and looked into a half-spherical dome 60 cm in diameter that could be rotated about his line of sight. The surface of the dome extended to the limits of the observer's visual field and was covered with a random pattern of coloured dots that contained no cues to gravitational orientation. The centre of the dome was fixed to the shaft of a DC torque motor (fig. 2); 30 cm in front of the observer was a circular target of 14 deg visual angle mounted on a coaxial shaft to a DC servo motor. The left half of the disc was white and the right half black, making a straight edge at the midpoint of which was a fixation spot. The angle of the disc and therefore of the black/white edge was controlled by the subject using a potentiometer. The output of the potentiometer was recorded on a strip chart recorder.

Static visual vertical was determined by means of 10 adjustments of the target disc from a random offset position to subjective vertical with the half spherical dome stationary. *Dynamic visual vertical* was determined by means of 10 continuous tracking experiments of the visual vertical for a 20 s stimulation period of either clockwise or counter-clockwise rotation of the dome at a constant angular velocity of 40 deg/s. A visual surround rotating around the observer's line of sight (roll motion) induced an apparent body rotation opposite in direction to pattern motion (rollvection) and caused a limited tilt of the subjective vertical (Dichgans *et al.*, 1974). The rationale for measurements of the dynamic visual vertical was that rollvection should make overt slight deviations of the visual vertical which might otherwise go undetected under purely static stimulus conditions.

CASE DESCRIPTIONS

Case 1

This patient was first seen when she was aged 18 yrs, 9 yrs following a severe head injury. Since then she had noted persistent vertical and horizontal diplopia with the false image to the right and above the true one. On examination she had a persistent tilt of the head of 15 to 20 deg to the right. Complex oculomotor abnormalities included the following: a left over right hypertropia in the primary position which increased with head tilt to the right and decreased to 3 deg with head tilt to the left (positive Bielschowsky head tilt test plus skew deviation); counter-clockwise cyclodeviation of the 12 o'clock meridian of each eye giving 20 deg of excyclotropia on the right and 2 deg of incyclotropia on the left (the difference caused by a partial left fourth nerve palsy); right beating jerk nystagmus with the eyes closed; horizontal monocular pendular nystagmus of the left eye in the primary position and activated by leftward gaze; bilaterally saccadic horizontal pursuit; diminution of left beating (fast phases) optokinetic nystagmus (full field stimulation, 60 deg/s); dynamic overshoot of leftward voluntary saccades. Other neurological abnormalities included a spastic quadriparesis, the abnormalities being more marked on the left than on the right, and left-sided cerebellar ataxia more marked in the lower than in the upper limb. Sensory examination was normal.

Electrooculography showed a directional preponderance of caloric and rotational vestibular nystagmus to the right, and bilaterally impaired visual suppression of horizontal vestibulo-ocular reflexes. Other investigations revealed delayed late ipsilateral components of the left side in the orbicularis oculi reflex; delayed N20 of the somatosensory evoked potentials from stimulation of the left tibial nerve; and bilateral frontotemporal high voltage theta activity on EEG. A CT scan demonstrated diffuse brainstem and cerebellar atrophy with some high density lesions in the left cerebellar hemisphere. This makes it impossible to relate OTR to a defined midbrain damage in this case. Involvement of the midbrain tegmentum can be assumed clinically only by the left fourth nerve palsy (if it is not caused by peripheral damage) and the monocular horizontal pendular nystagmus, which is thought to be due to lesions close to the oculomotor nuclei (Gresty *et al.*, 1982). Brainstem auditory evoked potentials and Doppler ultrasound of the extracranial vessels were both normal.

Case 2

This 21-yr-old woman presented with a twelve-month history of vertical diplopia. Six years previously, following a brief history of headaches and seizures, she was found to have a grade I subependymal astrocytoma of the right ventricle. She had no neurological deficits before or after the operation. Three years following surgery she developed a recurrence of the tumour which caused an incomplete left homonymous hemianopia and was treated by cranial irradiation. Vertical diplopia first occurred 2 yrs after irradiation.

On examination at the age of 21 yrs we found the following complex oculomotor abnormalities: 3.5 deg of right over left hypertropia in the primary position which increased in leftward gaze but was unaffected by head posture; about 10 deg of clockwise cyclodeviation (roll) in each eye; a head tilt (and to a lesser extent a trunk tilt) of 25 to 30 deg to the left; almost complete paralysis of upward gaze (5 deg, saccades) and a lesser paresis of downward gaze (15 deg, saccades); spontaneous left-beating jerk nystagmus in the primary position; an asymmetric convergence nystagmus affecting the left eye more than the right on intended convergence; absent vertical and left beating optokinetic nystagmus (no slow phases with full-field stimulation, 60 deg/s) and severely reduced right-beating optokinetic nystagmus (slow phases preserved).

Other neurological findings included a moderately severe left hemiparesis affecting the face, arm and leg, and a neocerebellar ataxia of the left leg. There were no sensory defects. Electro-oculography showed a left-beating preponderance of caloric and rotational vestibular nystagmus. Other investigations included an audiogram which showed a high frequency sensorineural hearing loss more marked on the right than the left; a delay in components 3, 4 and 5 of the brainstem auditory evoked potentials from the right ear; and focal bitemporal activity in the EEG. A CT scan showed a cystic tumour rostral to the fourth ventricle infiltrating the right thalamus and the midbrain tegmentum, as well as the right parieto-occipital white matter.

Case 3

An 18-yr-old woman was referred with a six-week history of increasing headache, vomiting, horizontal diplopia and galactorrhoea. On examination she had bilateral papilloedema and a slight left abducens palsy. CT scan of the brain showed a tumour of the pineal region causing hydrocephalus with pineal calcification to the left of the midline. Following shunting of the right lateral ventricle a pilocytic astrocytoma of the pineal region was removed from the dorsal part of the third ventricle which extended to the midbrain tegmentum.

TABLE 1. OCULAR TILT REACTION (NEURO-OPHTHALMOLOGICAL DATA)

	Case	*Side of lesion*	*Head tilt*	*Skew deviation*	*Ocular torsion*		*Visual vertical*
1	Midbrain	(R)	15–20° R	3° L > R	RE: 15° ex	(LE: 2° in)*	+16.4°
2		(L)	25–30° L	7° R > L	RE: 10° in	LE: 10° ex	−15.2°
3		(L)	15° L	4° R > L	(RE: 15° ex)*	LE: 10° ex	−7.3
4	Lateral medulla oblongata	R	5° R	2–3° L > R	RE: 13° ex	LE: 0°	+5.3°
5		L > R	10° R	5–6° R > L	RE: 4° ex	LE: 20° ex	+14.4
6		L	30° L	5° R > L	RE: 0°	LE: 10° ex	−52.3
7		L	20° L	7° R > L	RE: 0°	LE: 20° ex	−12.5°

R = right, L = left, RE = right eye, LE = left eye; ex = excyclotropia, in = incyclotropia, + = clockwise rotation, — = counter-clockwise rotation, * = additional fourth nerve palsy. (R) (L) = in Cases 1–3 involvement of the contralateral midbrain tegmentum cannot be excluded.

Postoperative examination revealed complex oculomotor abnormalities: 10 deg of right over left hypertropia in the primary position increasing to 12.5 deg on head tilt to the right and decreasing to 7 deg on head tilt left (positive Bielschowsky head tilt test plus skew deviation); 15 deg of counterclockwise cyclodeviation of the right eye and 10 deg of clockwise cyclodeviation of the left eye; complete paresis of upward gaze from the primary position, with associated convergence nystagmus precipitated by downward optokinetic stimulation; bilaterally saccadic horizontal pursuit; absent vertical optokinetic nystagmus (no slow phases in vertical direction with full field stimulation 60 deg/s); impaired visual suppression of the vestibulo-ocular reflex. There was 15 deg of leftward head tilt, a leftward tilt of the trunk and slight ataxia of gait, but no motor or sensory deficits.

Cases 4–7

Four out of 11 patients referred with acute infarction of the dorsolateral medulla oblongata (Wallenberg's syndrome) showed a complete ocular tilt reaction in the acute stage of the syndrome. All patients (despite interindividual differences in the severity of the symptoms) were clinically characterized by ipsilateral limb dysmetria, Horner's syndrome, impairment of facial pain and temperature sensation, and paralysis of the palate, pharynx and larynx with dysphagia and dysphonia, as well as contralateral impairment of pain and temperature sensation over the trunk and limbs.

On examination of the 4 patients (all male, aged 42–75 yrs, mean 55 yrs), the lesion of the dorsolateral medulla was on the left side in Cases 6 and 7 and on the right in Case 4. The angle of ipsilateral head and trunk tilt relative to the true vertical varied from 5 to 30 deg; the contralateral over ipsilateral hypertropia varied from 2 to 7 deg in the primary position. Cyclodeviation consisted of a monocular excyclotropia of the ipsilateral eye of 10 to 25 deg while the contralateral hypertropic eye was not rotated.

Case 5 was complicated in that an acute Wallenberg's syndrome on the left was admixed with an additional vascular pontomedullary lesion on the right (right sixth nerve palsy). Upbeat nystagmus that was present—not a typical sign of a unilateral Wallenberg's syndrome—can be explained by bilateral involvement of the caudal brainstem since upbeat nystagmus is an indicator of intra-axial lesions of either the pontomedullary or pontomesencephalic junction (Fisher *et al.*, 1983). This patient showed a right over left hypertropia, a 25 deg excyclotropia of the left eye without cyclodeviation of the hypertropic right eye but the 10 deg head tilt and the body lateropulsion were directed towards the right. The gradual improvement of OTR in the patients (Cases 4–7) varied from complete recovery within 20 days to an incomplete recovery with a slight residual OTR for more than 10 months (Table 2).

RESULTS

Deviation of Subjective Visual Vertical

Adjustments of the static visual vertical in normal subjects revealed deviations of less than 1 deg clockwise tilt from the true vertical within a stationary surround ($\bar{X}+0.96$ deg, SD ± 1.05). With roll motion to the right, the mean tilt of the visual vertical in the direction of pattern motion was +12.65 deg (SD ± 5.01); with rollmotion to the left, mean tilt was −10.54 deg (SD ± 5.66) as shown in fig. 3.

TABLE 2. ACUTE WALLENBERG'S SYNDROME WITH OCULAR TILT REACTION (OTR)

Case	*Day of first detection of OTR*	*Day of first determination subjective visual vertical**	*Day of fundus photographs and subjective visual vertical***	*Gradual recovery of OTR within*
4	10	12	12	~ 20 d
5	7	21	28	> 10 mos
6	1	1	19	~ 1 mo
7	2	3	37	> 6 mos

* *See* fig. 4; ** *See* fig. 6.

All 7 patients exhibited significant deviations of the static as well as the dynamic visual vertical in the direction of their spontaneous head tilt. In the patients with midbrain lesions, mean tilt angles within a static surround were 7.3 deg (SD ± 1.6) for Case 3, 15.2 deg (SD ± 2.1) for Case 2, and 16.4 deg (SD ± 1.2) for Case 1, when viewing just with the hypotropic eye (fig. 5), values similar to those obtained with binocular vision (fig. 3). Mean tilt angles when viewing with the hypertropic eye, however, were 3.9 deg for Case 3, 1.6 deg for Case 2, and 8.3 deg for Case 1, corresponding to the smaller angle of cyclodeviation.

All 4 patients with OTR due to infarction of the dorsolateral medulla oblongata (Cases 4–7) also exhibited significant deviations of the static subjective visual vertical in the direction of spontaneous head tilt ranging from 5.3 deg to 53.2 deg with binocular vision (figs 4, 6). With monocular vision the deviations of the static as well as the dynamic visual vertical for Case 7 were somewhat greater for the ipsilateral eye (static: 12.5 deg) as compared with the contralateral eye (9.2 deg).

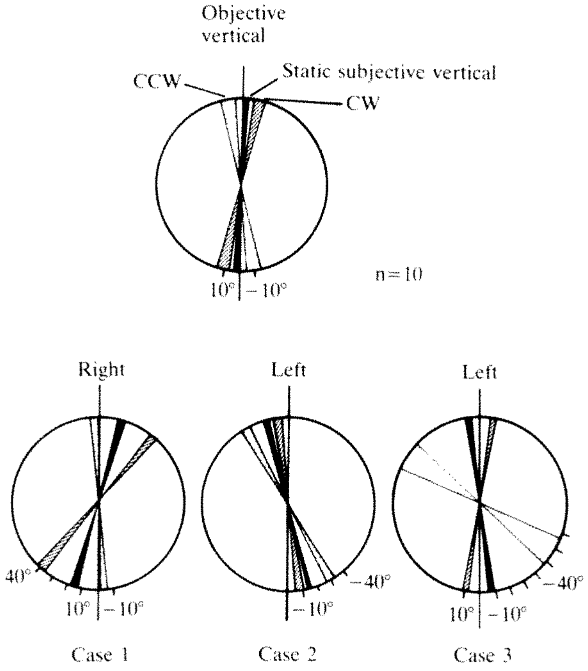

FIG. 3. Static and dynamic subjective visual vertical in 10 normal subjects (*top*) and 3 patients with an ocular tilt reaction due to chronic midbrain lesions (*bottom*). The hatched segments represent SDs of 10 individual adjustments with binocular vision (CW = clockwise rotation of the dome; CCW = counter-clockwise rotation of the dome). The 3 patients exhibit significant deviations of the static as well as the dynamic visual vertical in the direction of their spontaneous head tilt. Rotation of the dome (which induced rollvection of the body opposite to pattern motion) causes disproportionately greater deviations of the dynamic visual vertical with an obvious asymmetry for the tilt angles, this being the greatest when pattern motion was directed towards head tilt.

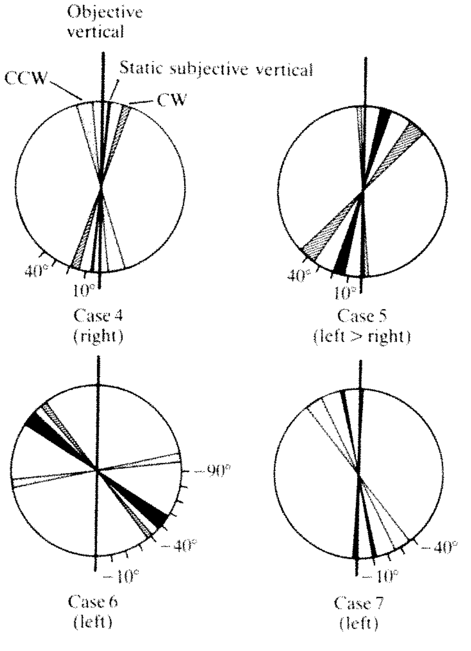

FIG. 4. Static and dynamic subjective visual vertical in 4 patients with a reversible tonic ocular tilt reaction due to infarction of the dorsolateral medulla oblongata (*Cases 4–7*). The hatched segments represent SDs of 10 adjustments with binocular vision. All patients exhibit a significant ipsilateral deviation of perceived vertical with disproportionately greater and asymmetric deviations of the dynamic visual vertical. Abbreviations as in fig. 3.

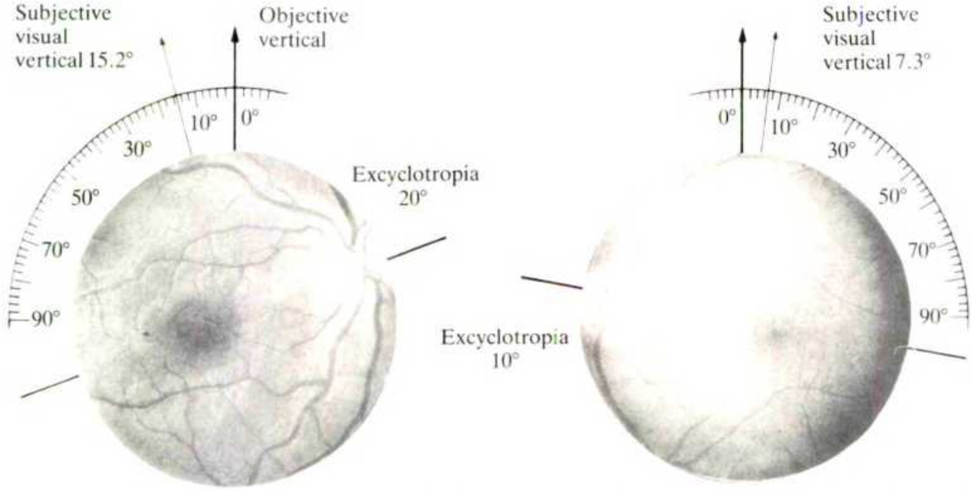

FIG. 5. Cyclodeviation of the hypotropic eye (fundus photographs with the head upright) and deviations of the static subjective visual vertical with monocular vision in *Case 1 (left) and Case 3 (right)*. Ocular tilt reaction is due to a chronic midbrain lesion in both cases. In order to make a quantitative comparison possible between the angles of excyclotropia and the perceived vertical, the adjustments of the subjective visual vertical were projected onto the fundus. The patients adjusted the subjective vertical to 15.2 deg clockwise (*Case 1*) and to 7.3 deg counter-clockwise (*Case 2*) (fig. 3). The tilt of the subjective vertical is greater with greater angles of excyclotropia, but there is no exact quantitative correspondence between the net tilt angles.

Constant velocity rotation (rollmotion) of the dome which induced rollvection of the body opposite to pattern motion caused a disproportionately greater deviation of dynamic vertical in all patients compared with normal subjects. This deviation of the subjective vertical, as in normal subjects, was always directed towards the pattern motion with an obvious asymmetry. Tilt angles were greatest when induced rollvection was directed opposite to ocular tilt reaction, i.e., clockwise pattern motion with counter-clockwise ocular tilt reaction and counterclockwise pattern motion with clockwise ocular tilt reaction (figs 3, 4).

DISCUSSION

We believe that the triad of head-trunk tilt, skew deviation, and ocular cyclodeviation can be attributed to a fundamental pattern of coordinated eye-head roll motion based upon afferent utricular/saccular as well as vertical canal input and may be elicited along the graviceptive pathways from the utricle via pontomedullary vestibular nuclei to the midbrain tegmentum. The tonic OTR thus elicited was different for the medullary lesions in that cyclodeviation was monocular (ipsilateral excyclotropia) and gradually improved within days to weeks. Spontaneous complaints about diplopia were surprisingly rare and mild. The particular synkinesis of OTR obviously is not only a pathological response either to electrical stimulation or lesional dysfunction but also represents physiological active

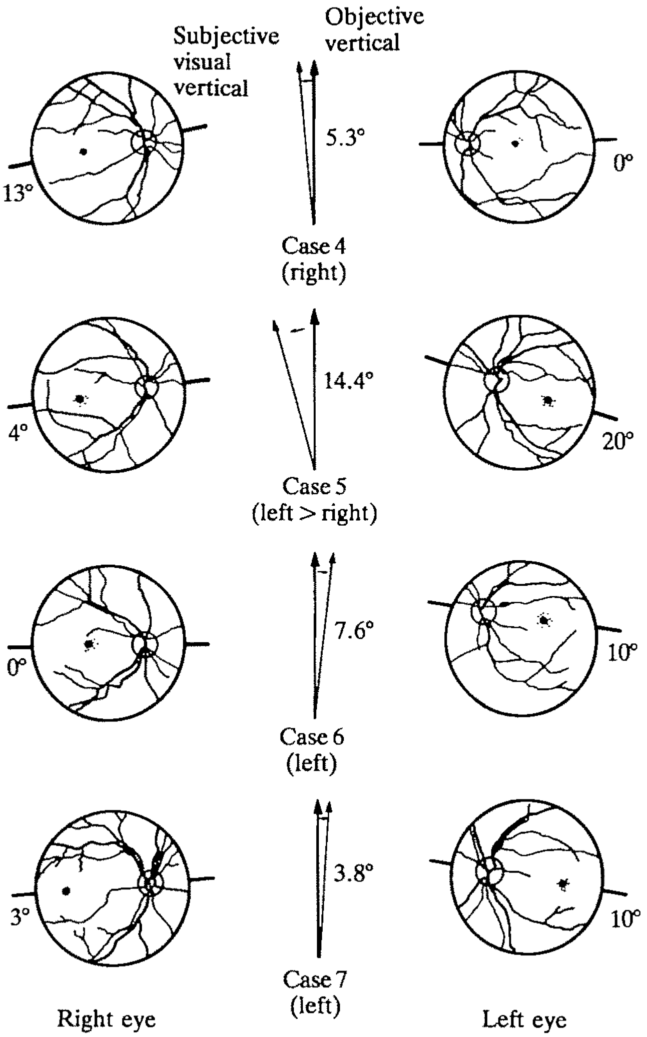

FIG. 6. Diagrams of fundus photographs with the head upright showing cyclodeviation and deviations of static subjective visual vertical on the same day (binocular vision) in 4 patients with tonic reversible ocular tilt reaction due to Wallenberg's syndrome (*Cases 4-7*). For comparison of the angle of cyclodeviation with the perceived vertical, the adjustments of the subjective visual vertical are projected onto the fundus (the patient's subjective vertical was adjusted in the opposite direction, as depicted here). There is a dysconjugate cyclodeviation with predominant excyclotropia of the ipsilateral hypotropic eye. The slight excyclotropia of the contralateral eye (up to 4°) is within the normal range. The direction of the deviation of the subjective vertical corresponds to the direction of spontaneous head tilt in *Cases 4, 6 and 7*. *Case 5* was complicated in that the left Wallenberg's syndrome was associated with an additional right pontine vascular lesion: the subjective visual vertical and the head were tilted opposite to skew deviation and excyclotropia.

eye-head coordination in the roll plane. Normally the tonic bilateral graviceptive input tends to stabilize eye and head in the upright position. A unilateral lesion causes an imbalance in vestibular tone in roll, a contralateral preponderance of the 'uprighting tone' with consequent ipsiversive OTR.

Topographical Specifity of Ocular Tilt Reaction

The anatomical region from which Westheimer and Blair (1975*a*, *b*) induced the ocular tilt reaction by electrical stimulation in the monkey was in the midbrain tegmentum dorsolateral to the third and fourth nuclei. It extended rostrally to include the nuclei of Cajal and Darkschewitsch as well as the walls of the third ventricle near the rostral cerebral aqueduct and caudally to the rostral parts of the floor of the fourth ventricle. Earlier stimulation experiments of the interstitial nucleus of Cajal, the pretectal area and the zona incerta in the cat evoked rotatory movements of the head in the frontal plane (Bartorelli, 1942) and conjugated cyclodeviation of the eyes when the head was held fixed (Hess *et al.*, 1946). Szentágothai (1943) had already considered the region of the interstitial nucleus of Cajal (INC) to be a centre of coordination of rotatory eye movements. Hyde and Toczek (1962) were able to show that rotational movements of the eyes and the head evoked by stimulation of the zona incerta in the cat depend on the functional integrity of ipsilateral INC. Cyclodeviation was significantly decreased or abolished after destruction in or medial to INC; head tilts in the frontal plane were significantly decreased after a lesion posteromedial to the INC.

Sano *et al.* (1972) reported either head extension (retroflexion) or ipsilateral head tilt in man (in cases of torticollis) induced by stereotaxic electrical stimulation of the INC or adjacent areas of the medial longitudinal fasciculus. Stimulation of the INC in one patient (with a history of posttraumatic see-saw nystagmus) activated or reproduced see-saw nystagmus with concurrent head tilt (probably a complete OTR) which was abolished by electrocauterization of this area. Stimulation of the area adjacent and caudal to INC resulted in head tilt solely. Thus until now the midbrain tegmentum around the INC was thought to be the critical structure in the elicitation of OTR. Since then 2 clinical cases of OTR have been reported as a paroxysmal disorder with concurrent oscillopsia secondary to brainstem lesions. The patient of Rabinovitch *et al.* (1977) suffered from MS and the paroxysmal OTR was associated with paroxysms of vertical and horizontal pendular nystagmus. The coincidence of these different attacks, as well as effective treatment with carbamazepine, suggests that the OTR in this case may be a variant of the paroxysmal attacks that occur in MS which have been suggested as being due to ephaptic conduction between adjacent demyelinated axons (Matthews, 1975; Osterman and Westerberg, 1975). The patient of Hedges and Hoyt (1982) had a focal brainstem abscess which involved the rostral midbrain and the area of the subthalamus and zona incerta ipsilateral to the direction of head tilt. The periodicity of the paroxysms in this case, occurring several times per hour and lasting 3 to 5 min, was also reminiscent of the above-mentioned paroxysmal brainstem attacks with some therapeutic benefit from the use of baclofen.

A nonparoxysmal tonic OTR persisting over months to years (Cases 1–3) has not been previously described for upper brainstem lesions, and neither a tonic nor a paroxysmal OTR has previously been described with lateral medullary brainstem lesions. The occurrence of OTR in Wallenberg's syndrome has hitherto escaped notice in the literature, although single components such as skew deviation and diplopia with tilted images (dissociated cyclodeviation) have been reported by Hagström *et al.* (1969) and Hörnsten (1974).

OTR in acute lateral medullary lesions is most probably caused by interruption of ascending otolith and posterior canal inputs near the vestibular nuclei and there is convincing evidence for OTR occurring with even more peripheral (labyrinthine) lesions. OTR or at least a combination of ipsilateral head tilt with skew deviation, was first suspected as a syndrome of peripheral labyrinthine dysfunction by Brain (1926) in a patient suffering from chronic nonsuppurative otitis media. In the case of Halmagyi *et al.* (1979), an ipsilateral transient tonic OTR was induced by inadvertent damage to one labyrinth leaving a partial utricular deficit which was the only obvious cause for the syndrome in that patient. The specific role of the utricle in the generation of OTR is supported by the earlier animal experiments of Suzuki *et al.* (1969) after electrical stimulation of single utricular nerves. They were able to induce cyclodeviation and concurrent vertical divergence and slight contralateral horizontal shifts of both eyes in the cat (spinal cord cut between C1 and C2 levels). With electrical stimulation action potentials are synchronized, rather than desynchronized as is the case with natural stimulation; the experimentally induced reaction thus showed contraversive cyclodeviation as well as a skew deviation determined by ipsilateral hypertropia and contralateral hypotropia. Accordingly, muscle tension increases and EMG responses of extraocular muscles were strongest in the ipsilateral superior oblique and contralateral inferior oblique.

Neurophysiologically the utricle projects to the lateral vestibular nucleus and to a minor extent to the superior vestibular nucleus. The synaptic organization of utricular input must provide patterns of activation for both spinal motoneurons (head tilt) and conjugate cyclodeviation with dysconjugate vertical divergence. Descending vestibulospinal projections from the lateral and medial vestibular nuclei and also descending projections in the medial longitudinal fasciculus (MLF) to the spinal cord are well known and several ascending pathways from the vestibular nuclear complex to the ocular motor nuclei have been confirmed by lesions and degeneration patterns as well as by use of axoplasmic tracers (Gacek, 1971, 1982; Lang *et al.*, 1979; Carpenter and Cowie, 1985). An ipsilateral projection from the superior vestibular nucleus follows the MLF and terminates in the ipsilateral fourth nerve nucleus, the bilateral oculomotor complex (inferior rectus subdivision), the ipsilateral nucleus of Darkschewitsch (probably not involved in eye movements), the ipsilateral INC and the rostral interstitial nucleus of the MLF (riMLF). Another ipsilateral projection originates from the lateral vestibular nucleus and terminates within the ipsilateral oculomotor complex via the ascending tract of Deiters. Finally, a contralateral projection primarily from the medial vestibular nucleus ascends in the MLF to terminate in the third, fourth, sixth and Darkschewitsch nuclei and in the INC. In order to generate the typical eye movements of the OTR, it could be argued that particular activation of the ipsilateral inferior rectus and inferior oblique (ipsilateral ascending tract of Deiters or via the ipsilateral

MLF?) as well as the contralateral superior rectus and superior oblique (contralateral ascending tract within MLF) are required (fig. 7). However, in contrast to the findings of Gacek (1971), there is experimental evidence that the ascending tract of Deiters is not involved in vertical eye movements but conveys information for the medial rectus subdivision (Reisine and Highstein, 1979; Lang *et al.*, 1979; Carpenter and Carleton, 1983).

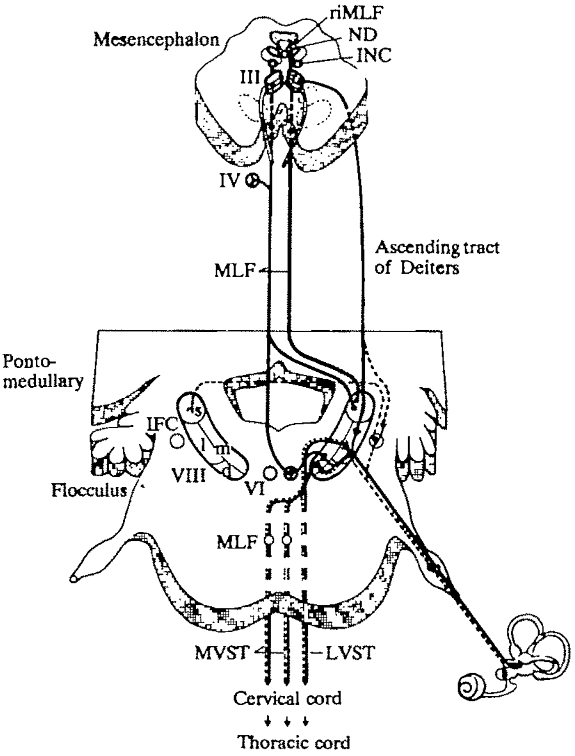

FIG. 7. Schematic drawing of graviceptive pathways probably involved in the generation of the ocular tilt reaction. The characteristic eye movements can be activated by utricular input via the ipsilateral MLF (mainly the ipsilateral inferior rectus and inferior oblique) and via the contralateral ascending tract within the MLF (mainly contralateral superior rectus and superior oblique). The ascending tract of Deiters most probably projects on to medial rectus subdivision. ND = nucleus of Darkschewitsch; INC = interstitial nucleus of Cajal; riMLF = rostral interstitial nucleus of the MLF; MLF = medial longitudinal fasciculus; IFC = infracerebellar nucleus; MVST = medial vestibulospinal tract; LVST = lateral vestibulospinal tract; s, l, m, d = superior, lateral, medial, and descending vestibular nuclei. Utricle (solid line), saccule (dashed line).

The INC has monosynaptic excitatory and inhibitory connections to fourth nerve motoneurons, a synaptic organization required of an integration centre for reciprocal control of vertical and rotational eye movements (Schwindt *et al.*, 1974). The INC may also coordinate eye and head tilt in roll by virtue of its afferent monosynaptic projections not only to the ocular but also to spinal motoneurons (King *et al.*, 1980). Although its function is not yet fully understood, it is thought to be involved in the vertical vestibulo-ocular reflex since downward postrotatory nystagmus was abolished after unilateral lesions (King *et al.*, 1981).

With respect to the neuronal mechanisms subserving the directional synergy of eye and head rollmotion, second-order type I vestibulospinal neurons are insufficient candidates because of the crossed vestibulocollic reflex connection. But ipsiversive coupling of eye and head could be mediated by excitatory ipsilaterally projecting tectoreticulospinal neurons as described by Berthoz and Grantyn (1986). These authors have shown that the complex axonal branching as well as the intense bursts associated with contraversive saccades and contralateral neck EMG during visual orientation of the animal are compatible with eye-head synkinesis in roll.

Hypothetically, the typical ocular pattern of OTR in Wallenberg's syndrome (skew deviation with monocular excyclotropia of the ipsilateral hypotropic eye) can be explained by a circumscribed lesion of the ascending pathways of the ipsilateral posterior semicircular canal. The neuronal network mediating the vestibulo-ocular reflex of the vertical canals is based upon sensory convergence within a three-neuron reflex arc. It links a set of extraocular muscles with their primary action aligned to the particular spatial plane of either the anterior or posterior canal. Sensorimotor transformation from canal planes to the planes of eye movements has been demonstrated at the level of second-order neurons within the vestibular nuclei. These neurons, projecting to oculomotor neuron pools, always contact their two respective principal eye movers in the excitatory as well as in the inhibitory (push-pull operational mode) vestibulo-ocular motor link (Graf *et al.*, 1983; Graf and Ezure, 1986). The posterior canal has excitatory connections to the ipsilateral

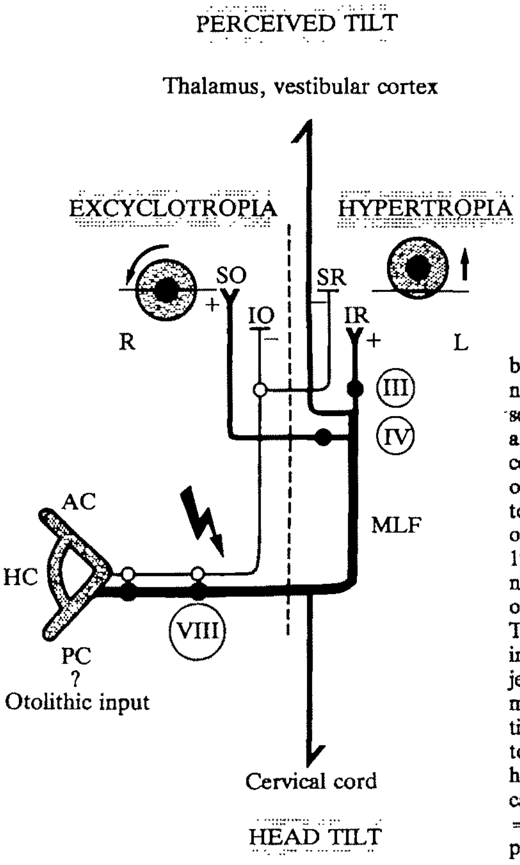

FIG. 8. Hypothetical explanation of OTR in Wallenberg's syndrome. Schematic representation of the three-neuron vestibulo-ocular reflex arc between posterior semicircular canal and extraocular eye muscles. It probably also conveys otolith information. An excitatory ascending pathway is linked to the ipsilateral superior oblique and the contralateral inferior rectus; an inhibitory ascending pathway is linked to ipsilateral inferior oblique and contralateral superior rectus (Graf *et al.*, 1983; Graf and Ezure, 1986). A lesion of these pathways near the vestibular nuclei complex causes excyclotropia of the ipsilateral and hypertropia of the contralateral eye. This pattern reflects ocular motor abnormality of OTR in Wallenberg's syndrome. Concurrent deviation of subjective visual vertical as well as head tilt could be mediated by ascending perceptual pathways to the vestibular cortex and descending vestibulospinal pathways to the upper cervical cord, respectively. HC, AC, PC = horizontal, anterior and posterior semicircular canals; MLF = medial longitudinal fasciculus; SO, IO = superior and inferior oblique muscles; SR, IR = superior and inferior rectus muscles.

superior oblique and the contralateral inferior rectus muscles (fig. 8). Simultaneously inhibitory pathways reach the ipsilateral inferior oblique and the contralateral superior rectus muscles. Thus a lesion of these pathways (which probably also convey otolith input) would cause excyclotropia of the ipsilateral eye as well as skew deviation with elevation of the contralateral eye. If the lesion damages both posterior and anterior canal pathways then complete OTR would result with hypotropia of the ipsilateral eye, hypertropia of the contralateral eye, and conjugated cyclorotation towards head tilt.

Alternating Skew Deviation, See-Saw Nystagmus and Ocular Tilt Reaction

Skew deviation or the Hertwig-Magendie syndrome is a relatively common supranuclear vertical divergence of the eyes associated with lesions in the posterior fossa, particularly those involving the brainstem tegmentum (Smith *et al.*, 1964; Keane, 1975). In about 12% of the patients with skew deviation, a confusing alternating hypertropia on lateral gaze to either side, or a spontaneous slowly alternating skew deviation, is observed, which resembles both see-saw nystagmus and the OTR (Corbett *et al.*, 1981; Mitchell *et al.*, 1981; Keane, 1985).

The eye movements in alternating skew deviation are slow, as distinct from the more rapid lesser-amplitude see-saw nystagmus which is basically a combination of alternating skew deviation mixed with alternating cyclodeviation (intorsion of the rising eye and extorsion of the falling eye) without head tilt. See-saw nystagmus has been reported with lesions of the diencephalic-mesencephalic junction (Daroff, 1965; Schmidt and Kommerell, 1974) and alternating skew deviation, frequently associated with elements of the sylvian aqueduct syndrome, is attributed to pretectal brainstem lesions (Corbett *et al.*, 1981; Mitchell *et al.*, 1981). Alternating skew deviation was elicited in man by a small unilateral pretectal stereotactic lesion (Nashold and Seaber, 1972) but most clinical cases suggest bilateral involvement. Such pretectal lesions compound the problem of distinguishing clinically skew deviation from subtle third and fourth nerve lesions, especially alternating adduction hypertropia from bilateral fourth nerve palsy (Keane, 1985). The combination of skew deviation with cyclodeviation has not yet been convincingly investigated, since Trobe (1984), in his study on cyclodeviation in acquired vertical strabismus, excluded all cases of skew deviation with a positive Bielschowsky's head tilt test. On the other hand, the Bielschowsky head tilt test cannot differentiate supranuclear from infranuclear bilateral fourth nerve palsy if alternating skew deviation results from a lesion of the utricular pathway with bilateral supranuclear paresis of either the superior or the inferior oblique muscles (Keane, 1985).

In experimental OTR a typical response to electrical stimulation in the monkey exhibits a 20 deg cyclodeviation which is equal in both eyes, coupled with an 8 to 10 deg vertical divergence (Westheimer and Blair, 1975*a*, *b*). A dysconjugate cyclodeviation with predominant excyclotropia of the ipsilateral hypotropic eye was a regular feature of the 4 patients that we observed with an OTR consequent to infarction of the dorsolateral medulla (fig. 6). Whether this monocular excyclotropia in Wallenberg's syndrome is due to specific damage near the vestibular nuclei which selectively affects ascending excitatory projections to the ipsilateral superior oblique muscle and inhibitory projections to the ipsilateral superior oblique muscle (fig. 8) must remain a matter for speculation. In tonic OTR the direction of eye torsion represents a pattern of extraocular eye muscle activation clearly opposite to the vestibulo-ocular reflex of human ocular counter roll, which tends to compensate for about 10% of static head tilt (Collewijn *et al.*, 1985). It has been observed that during voluntary dynamic head tilt, ipsiversive saccadic torsional eye movements precede head motion (Jampel, 1981) and, with respect to this, OTR resembles prolonged intended head tilt. The convergence nystagmus of 2 of our patients with midbrain lesions (Cases 2, 3) may correspond to the small horizontal convergence movements of the stimulated monkeys in the experiments of Westheimer and Blair (1975*a*, *b*).

In the case of Halmagyi *et al.* (1979) with a partial utricular lesion and in the patients with acute Wallenberg's syndrome (Cases 4–7) and in the patients with midbrain lesions (Cases 1–3, in which bilateral midbrain lesions cannot be excluded), OTR was ipsilateral to the side of the lesion as was mostly the case in the stimulation experiments by Westheimer and Blair (1975*a*, *b*) in the monkey. The direction of OTR due either to stimulation or lesioning remains confused and may involve different ipsilateral as well as contralateral pathways with either excitation, inhibition or disinhibition. It may be speculated that OTR on electrical stimulation is caused by artificial direct activation of efferent pathways. OTR due to clinical lesions of afferent utricular pathways represents an ipsiversive motor compensation of an apparent contraversive eye-head roll motion. Surprisingly there was no central compensation of the syndrome (which lasted for months to years) in our patients with chronic midbrain lesions as distinct from peripheral labyrinthine dysfunction. In the patients suffering from Wallenberg's syndrome OTR gradually improved within days to months.

Subjective Visual Vertical in Ocular Tilt Reaction

The significant tilt of the subjective visual vertical towards the head tilt in all but 1 patient (even with the head objectively upright) suggests that this is the perceptual correlate of an apparent body tilt relative to true earth coordinates. An inclination must be involved of the internal representation of the gravitational vector which causes both to appear tilted contraversive to the lesioned side, the seen environment and posture. This determines perception as well as postural control with the consequences of a compensatory ipsiversive eye head tilt, the OTR (fig. 9). Despite the resulting postural imbalance and despite the visual reference of objective vertical, the eyes, head and body are adjusted to what the CNS computes as being vertical.

Different brainstem lesions from midbrain to medulla cause ipsiversive deviation of subjective visual vertical (Friedmann, 1970) which in our experience may be independent from the OTR and eye torsion as can be seen in Case 5. The amount of the tilt of subjective vertical under static stimulus conditions was greater for the hypotropic eye, which also showed greater angles of cyclodeviation. There is, however, no close correlation between the net tilt angle of the particular cyclorotation and the visual vertical in one eye.

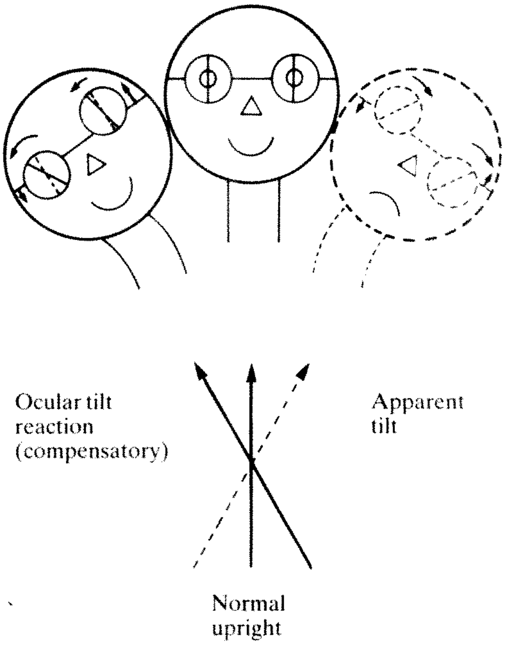

FIG. 9. Ocular tilt reaction represented as a 'motor compensation' of a lesion-induced apparent eye-head tilt (dashed line), and which would be opposite in direction to the apparent tilt. Eyes and head are continuously adjusted to what the lesioned brain computes as being vertical.

Both the patients with midbrain lesions and those with lateral medullary lesions exhibited a striking asymmetry of the dynamic visual vertical with the greater deviation towards head tilt. These results are compatible with earlier data on physiological optokinetic-graviceptive interaction in different head tilt positions obtained by means of a comparable stimulus display (Dichgans *et al.*, 1974). In normal subjects, deviation of the subjective vertical by roll motion increases progressively with larger head tilt angles. The effect is asymmetric, with a maximal deviation if the visual stimulus rotates opposite to actual head tilt. Under natural conditions, head tilt causes relative motion of the visual scene opposite in direction. The explanation for the asymmetry of the effects is that relative motion in this case will correspond to information from graviceptors (greater deviations), whereas with the two motions going in the same direction, visual information would conflict with graviceptive input (smaller deviation). The asymmetry of adjustments of the dynamic visual vertical in patients displaying an OTR suggests that, even with the head fixed in the true vertical, they perceive their heads as actually tilted opposite to the direction of the tilt reaction.

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BILATERAL OCCLUSION OF THE INTERNAL CAROTID ARTERIES

PRESENTING SYMPTOMS IN 74 PATIENTS AND A PROSPECTIVE STUDY OF 34 MEDICALLY TREATED PATIENTS

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SUMMARY

The presenting characteristics of 74 patients with atherosclerotic occlusion of both internal carotid arteries are described. All had suffered either ischaemic hemisphere infarcts (80%) and/or transient ischaemic attacks (80%) involving one (78%) or both (22%) carotid territories. In addition, 10 subjects (14%) incurred recurrent vertebrobasilar or presyncopal episodes, many of which appeared secondary to haemodynamic insufficiency. The incidence of risk factors and concomitant vascular disease was high; 93% gave a history of heavy smoking.

Thirty-four subjects were treated conservatively and followed prospectively for a mean of 42 months. Eighteen patients (53%) suffered further cerebrovascular events, an ischaemic event rate of 15% per patient per year. These were isolated transient ischaemic attacks (TIAs) in 7 and stroke in 11 patients. The latter suffered a total of 15 strokes during the follow-up period of 42 months; the annual stroke rate was 13% per patient year. Patients who had presented with ischaemic events involving more than one carotid territory were significantly more prone to subsequent cerebral infarction than those in whom symptoms had been confined to one territory ($P < 0.05$). None of the 5 patients with haemodynamic TIAs who were managed conservatively developed a stroke during the follow-up period and their symptoms remitted spontaneously. Deaths per year amounted to 8%. Twenty-four patients (71%) survived, of whom half were either symptom-free or minimally disabled.

In this group of preselected patients, which excludes those with severe deficits at presentation, bilateral occlusion of the carotid arteries may be a condition compatible with useful existence.

INTRODUCTION

Fisher (1954), in his exhaustive study of the cerebral vessels in 432 consecutive postmortem examinations, discovered bilateral carotid artery occlusion (BCAO) in 11 subjects. All had severe neurological deficits during life which, if not solely responsible for, at least contributed to the cause of death. Clarke and Harrison (1956) emphasized the poor outcome with a description of rapid cognitive decline and evolving neurological deficits in 2 subjects with almost complete occlusion of

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the carotid arteries, again diagnosed at autopsy. The picture changed, however, when angiography became widely established as a means of examining the cerebral circulation during life and in 1960, Groch *et al.* reported the case of a 37-year-old woman with BCAO who remained well during a three year follow-up period. Subsequent studies by Fields *et al.* (1961), Hardy *et al.* (1962), Wortzman *et al.* (1968) and Waltimo and Fogelholm (1975) have added a total of 58 cases to the literature, of which 21 died within months of diagnosis, 16 were or became severely disabled by a combination of focal deficits and intellectual decline and 21 remained well with minor disability. They continued to do so for a mean period of fifty months in the two studies which provided extended follow-up data (Hardy *et al.*, 1962; Waltimo and Fogelholm, 1975). None of these studies, however, was designed to evaluate the nature of cerebrovascular events occurring during follow-up and none was a prospective study following a well-designed protocol to ensure completeness of data.

Symptoms of recurrent retinal and hemisphere ischaemia may continue after the demonstration of BCAO and controversy persists about the relative importance of embolic and haemodynamic phenomena. We describe the presenting characteristics of 74 patients with BCAO which represents the largest series to appear in the literature. Thirty-four subjects were treated conservatively and followed prospectively for a mean of forty-two months. The data has been analysed in an attempt to define the mechanism of subsequent deterioration.

PATIENTS

All the patients with BCAO who fulfilled the entry requirements for the Cooperative Study of Extracranial/Intracranial Arterial Anastomoses (EC/IC Bypass Study) were considered for entry into the present study (EC/IC Bypass Study Group, 1985).

Patients must have had an ischaemic event (either TIA or completed stroke) in the carotid distribution, within three months of entry into the study. Subjects had to be able to give informed consent and be capable of self-care for most of the activities of daily living. Those with more than moderate disability and without useful residual function in the affected territory or with cerebral haemorrhage were excluded.

Out of a total of 1377 patients deemed eligible and entered into the trial, 74 had BCAO at entry. A total of 43 patients was allocated to the medical group, but 9 were excluded from the outcome of medical treatment analysis because of some type of surgical intervention. The protocol of the parent study (EC/IC Bypass Study Group, 1985) did not prohibit surgery on the nonrandomized side; 3 patients had an EC/IC bypass performed on the asymptomatic side as a 'prophylactic' measure and 1 patient underwent the procedure on the previously asymptomatic side because of progressively deteriorating vision. The remaining 5 patients were excluded because they had external carotid endarterectomies shortly after entry. A separate analysis of the 9 subjects confirmed that their exclusion did not bias the results in favour of better prognosis.

METHODS

A detailed history and examination were recorded on standardized forms at entry. In addition, a 12-point functional assessment was included and 2 items (the ability to shop and work unaided) have been used in the present study. Details of various risk factors (hypertension, diabetes, heart disease, smoking habits) were included and the following investigations were obtained; Hb, random blood glucose and fasting cholesterol concentrations, ECG (for evidence of left ventricular hypertrophy, previous myocardial infarction and rhythm disturbances), chest x-ray and, where available, CT scan. The angiogram was required to demonstrate at least the extracranial and intracranial carotid arteries, the middle cerebral arteries and the extracranial external carotid arteries. Angiography of the vertebrobasilar circulation was not demanded. Copies of the angiograms were available as they were sent to the coordinating centre for a standardized evaluation.

All patients were seen by the participating neurologist at their centre six weeks after entry and at three-monthly intervals thereafter. An interim history and examination was documented at each visit. All patients were prescribed aspirin, 325 mg four times per day throughout, unless specifically contraindicated. The control of blood pressure was encouraged and monitored throughout the duration of the period of the referring centre.

TABLE 1. PRESENTING CHARACTERISTICS OF PATIENTS WITH BCAO (n = 74)

Age (mean, in yrs)	57, SD 8 (range 32–76)
Sex:	
Male	66
Female	8
Race:	
Caucasian	68
Black	2
Oriental	4
Duration of symptoms of cerebrovascular disease before entry (months)	24 (range 3 days–76 months)

RESULTS

Analysis of Presenting Data

Patient details and risk factors. Presenting characteristics of all patients with BCAO (n = 74) who entered the present study are summarized in Table 1. Table 2 details the incidence of risk factors and associated vascular disease. Twenty-eight patients (37.8%) were hypertensive as judged by history and/or examination, and of these 18 were receiving regular medication. Ten patients had diabetes mellitus which was being treated by diet plus hypoglycaemic drugs in 7, and insulin in 3. Fifty-nine patients were currently smoking cigarettes, 4 had stopped just before entry and a further 6 had given up more than five years before. Only 5 subjects had never smoked habitually. Of the 63 subjects (93%) who were or had been regular smokers, the average consumption was 20 cigarettes daily for forty-four years. Nine subjects did not have hypertension, a past history of myocardial infarction, claudication, diabetes or an elevated cholesterol level but they were all heavy smokers at the time of entry.

Presenting symptoms. Fifty-nine (80%) patients out of the total of 74 had suffered

TABLE 2. INCIDENCE OF RISK FACTORS AND ASSOCIATED VASCULAR DISEASE IN PATIENTS WITH BCAO (n = 74)

	Number (% of total)
Hypertension (by history and/or BP 160/90 mmHg)	28 (37.8)
Myocardial infarction (by history and/or ECG)	6 (8.1)
Angina	16 (21.1)
Intermittent claudication	9 (12.2)
Diabetes mellitus	10 (13.5)
Smoking:	
Never	5 (7.3)
Stopped more than 5 yrs before	6 (8.8)
Currently smoking or recently stopped	63 (85.1)
Serum cholesterol:	
> 7.2 mmol/l	17 (25.0)
< 7.2 mmol/l	49 (66.2)
Not done	8 (10.8)
None of the above	0 (0)

TABLE 3. SYMPTOMS OF CEREBROVASCULAR DISEASE IN PATIENTS WITH BCAO AT PRESENTATION (n = 74)

	Number
Total number of patients with stroke(s)	59
Territory involved:	
Right carotid	26
Left carotid	27
Bilateral carotid	6
Vertebrobasilar	0
Total number of patients with TIAs	59
Most frequent distribution of TIAs:	
Right carotid (retinal as % of total)	27 (14.8)
Left carotid (retinal as % of total)	25 (28.0)
Nonhemisphere*	7
Ischaemic symptoms (stroke and/or TIA)	
Confined to one carotid	48
Confined to both carotids	16
Carotid and nonhemisphere	10

* This term receives further clarification in the text. Note that the total number of patients with nonhemisphere TIAs was 10 but in 3 subjects they occurred in conjunction with more frequent carotid territory TIAs.

one (n = 45) or more (n = 14) completed strokes at the time of presentation (Table 3). The maximum number of strokes suffered by one patient before presentation was four. The strokes usually involved the cerebral hemispheres (n = 71), occasionally the retina (n = 3), but in no case was the brainstem the site of insult.

TABLE 4. CLINICAL STATUS OF PATIENTS WITH BCAO AT PRESENTATION (n = 74)

	Number (% of total)
Neurological examination:	
Normal	21 (28.4)
Abnormal	53 (71.6)
Working:	
Stopped due to retirement or illness other than CVD	23 (31.1)
Stopped due to CVD	12 (16.2)
Working with difficulty/needing help	10 (13.5)
Working without difficulty	29 (39.2)
Shopping:	
With difficulty/needing help	23 (31.1)
Without difficulty	51 (68.9)
Mentation:	
Normal	65 (87.8)
Impaired	9 (12.2)
Seizures:	
Focal motor	3 (4.0)
Generalized	0

Fifty-nine (80%) subjects had a history of one or more TIAs, involving territories supplied by the carotid arteries in 52 patients. In the remaining 7 subjects, the transient episodes were nonhemispheric (*see* below). TIAs were the sole presenting feature in the 15 (20%) subjects who gave no history of stroke. Ten of the 59 subjects with TIAs suffered recurrent episodes in more than one vascular territory. The number of TIAs varied considerably; 33 patients suffered 5 or less, 20 cases incurred between 5 and 50, and 6 subjects had more than 100 attacks.

Ischaemic symptoms (stroke and/or TIA) were confined to the territory supplied by one carotid artery in 48 subjects (64.9%) and involved the distribution of both carotid arteries in 16 (21.6%). In the remaining 10 cases (13.5%), recurrent nonhemisphere symptoms, which appeared haemodynamic, were also a feature and are described below.

Clinical status. Neurological examination was normal in 21 patients (28.4%) and abnormal in 53 (71.6%) at the time of presentation (Table 4). Twelve patients were unemployed as a direct consequence of cerebrovascular disease and a further 23 had stopped working because of other illness or retirement. Of those still at work (n = 39) (52.7%), over half were coping without difficulty; 51 (68.9% of the total) could manage their shopping unaided, but the remaining 23 subjects (31.1%) found it difficult or needed assistance.

Mentation was described as impaired in 9 subjects (12.2%). Two of these were emotionally labile, dysarthric and tetraparetic as a result of bilateral hemisphere infarcts. Six had large left middle carotid artery territory infarcts clinically and confirmed by CT, of whom 5 were dysphasic. The remaining patient presented with a left hemiparesis and visuospatial disturbances due to infarction involving the right middle cerebral artery territory; a CT scan demonstrated generalized atrophy as well as a large infarct in the territory of the right middle cerebral artery. Three subjects suffered recurrent motor seizures, in 2 of whom there was a CT lesion in the appropriate area.

TABLE 5. SYMPTOMS POSSIBLY RELATED TO HAEMODYNAMIC DISTURBANCES IN 10 PATIENTS WITH BCAO AT PRESENTATION (n = 74)

Vertebrobasilar TIAs* induced by standing or neck extension	5
Vertebrobasilar TIAs not related to postural change	1
Presyncopal symptoms on standing	3
Drop attacks only	1
Paroxysmal upper limb dyskinesia	2
Venous stasis retinopathy	1

* As defined by the Ad Hoc Committee (1975)

'Haemodynamic' nonhemisphere symptoms. Ten patients had symptoms which suggested a haemodynamic aetiology (Table 5). In 6, the symptoms were those of recurrent brainstem ischaemia, fulfilling the clinical criteria suggested by the Ad Hoc Committee (1975). Two suffered visual blurring, vertigo and ataxia, 2 others had dysarthria and bilateral leg weakness and the remaining 2 suffered visual diminution, ataxia and drop attacks. In 5 of these subjects, a definite relationship to postural change emerged with episodes occurring predictably on standing or neck extension. These triggers were not apparent in the sixth patient with classical episodes of brainstem ischaemia but angiography of the vertebrobasilar system in this patient was normal. Another 3 subjects suffered presyncopal symptoms with dizziness, a feeling of faintness and visual blurring on standing. One patient gave a three-month history of recurrent drop attacks again precipitated by standing. Examination of another patient revealed signs of venous stasis retinopathy and he also suffered posturally-induced vertebrobasilar TIAs. Paroxysmal jerking of an upper limb was reported by 2 patients; again, this only occurred on standing when it was associated with presyncopal symptoms in 1 case and well-defined brainstem symptoms in another. Six of the 10 patients had vertebral as well as carotid

angiography. No posterior circulation disease was demonstrated in 5, and in the sixth, there was proximal occlusion of the left vertebral, mild stenosis of the right vertebral and a normal basilar artery.

Analysis of Follow-up Data

Overall outcome. Thirty-four patients treated conservatively for BCAO were followed for a mean period of 42 months (range 4–77 months) as shown in Table 6. Six subjects died from unrelated causes (myocardial infarction 3, trauma 2, gastrointestinal bleeding 1), 1 of whom had a stroke in the period between entry and death. Eleven patients suffered recurrent cerebral infarction(s), of whom 4 died as a consequence. Seven subjects suffered recurrent TIAs but no further strokes and no neurological decline. The remaining 11 patients were free of all recurrent cerebral ischaemic events throughout the follow-up period. The 24 survivors (71%) were followed for a mean duration of 52 months (range 32–77).

TABLE 6. OUTCOME OF 34 PATIENTS WITH BCAO TREATED CONSERVATIVELY*

	Number (% of total)
Stroke related death	4 (11.8)
Suffered stroke(s) but alive	6 (17.6)
Death from: Trauma (2) Myocardial infarction (3)** Gastrointestinal haemorrhage (1)	6 (17.6)
Recurrent TIA(s) but no stroke: Hemisphere and/or retinal (4) Nonhemisphere (3)	7 (20.6)
No cerebral ischaemic events	11 (32.4)

* Mean duration of follow-up 42 months, range 4–77 months. ** One of these subjects suffered a stroke during follow-up

Incidence and type of stroke. Eleven (32.3%) of the patients suffered 15 strokes during the follow-up period of 42 months, so the annual stroke rate was 12.6% per patient year. Recurrent strokes involved a single hemisphere in 10 subjects and probably did so in the eleventh but in that particular case, clinical details of the terminal illness were inadequate and no postmortem examination was obtained. In the 10 subjects where clinical localization was certain, the previously symptomatic hemisphere was affected in 4 patients; in 4 cases, both hemispheres had previously been symptomatic, and delayed stroke affected a previously asymptomatic hemisphere in 2 cases.

Completed stroke was heralded by the recurrence of TIAs, involving the appropriate territory, in 2 patients, but no such warning was apparent in 6 cases. The 3 remaining subjects had continued to suffer infrequent TIAs throughout follow-up, occurring in the territory appropriate to the subsequent stroke.

Incidence and type of TIA. Twelve subjects (35.3%) suffered 1 or more TIAs during follow-up. These were of a focal nature and involved the hemisphere and/or retina in 9 cases and were not localized to the cerebral hemispheres in 3 patients, 1 of whom also suffered recurrent episodes of transient monocular blindness. Posturally-induced triggers were historically apparent in the 3 subjects with recurrent nonhemisphere episodes (vertebrobasilar TIAs 2, presyncope 1) and in 1 subject with paroxysmal upper limb dyskinesia. Another subject developed recurrent monocular blindness precipitated by light, suggesting retinal hypoperfusion. Thus haemodynamic factors appeared important in 5 out of the total of 12 subjects with recurrent TIAs. Recurrent TIA was not in itself a bad prognostic feature since 7 of the 12 subjects remained well apart from TIAs throughout the period of follow-up. Four of the 5 patients with 'haemodynamic' TIAs remitted spontaneously and did not develop a stroke; the fifth patient (recurrent upper limb dyskinesia which also remitted) died of a gastrointestinal haemorrhage, possibly related to aspirin, at 53 months. Haemodynamic factors were not historically apparent in the 5 patients with recurrent TIAs (hemisphere localization in each case) who went on to suffer a delayed stroke.

Angiographic appearances in patients suffering recurrent ischaemic events. The angiograms performed at entry into the study on the 11 subjects who suffered a stroke during the follow-up period were reviewed. Severe stenosis of the external carotid artery on the side appropriate to the stroke was apparent in 1 case and moderate stenosis in 4 cases, but in the remaining 6 subjects, this artery was considered normal or only mildly stenosed. The common carotid artery was not significantly stenosed on the appropriate side in any of the 11 subjects with delayed stroke. In the 4 subjects suffering recurrent hemisphere and/or retinal TIAs but no subsequent stroke, hemisphere events occurred on the side ipsilateral to a diseased external carotid artery in 2 patients. Thus of the 15 subjects with delayed hemisphere ischaemic events (stroke and/or TIA), 6 had moderate, and 1 severe, stenosis of the ipsilateral external carotid artery. In the 16 subjects who did not suffer any delayed ischaemic episodes, 4 had moderate stenosis of one external carotid artery. This difference in incidence of external carotid disease does not achieve statistical significance. The proximal stumps of the occluded internal carotid arteries were also reviewed in the 11 subjects with recurrent stroke, and in 2 cases the stump was irregular and considered to harbour a thrombus on the appropriate side. The stump had a smooth outline in the remaining 9 subjects. Two of the 4 patients with delayed hemisphere TIAs but no stroke had an irregular appearance to the stump, although this was not thought to be a thrombus. Of the 32 stumps in the 16 patients who suffered no cerebral ischaemic events during follow-up, 2 had an appearance compatible with thrombus. Again, the difference in incidence of 'stump thrombus' did not achieve statistical significance.

Four vessel angiography was undertaken in 10 out of the 18 patients with delayed ischaemic events and in the remaining 8 cases, the investigation was limited to the carotid arteries. The collateral supply was considered adequate in 9 patients in that good filling of the terminal internal carotid arteries was seen. In the remaining 8 subjects, the terminal internal carotid arteries were not seen but the study was limited in 5 and therefore no general statement regarding the collateral supply in patients who suffer delayed ischaemic events could be made. Thus in the context of the present study, the angiogram was not a useful indicator likely to differentiate between good and poor outcome.

TABLE 7. ENTRY CHARACTERISTICS AS A PROGNOSTIC INDICATOR DURING FOLLOW-UP (MEAN DURATION 42 MONTHS) IN PATIENTS WITH BCAO ($n = 34$)

	Stroke (7) and deaths due to stroke (4)	*TIA only (7) or no cerebral ischaemic events (16)*
Total	11	23
Age at entry (yrs)	59 (52–67)	57 (32–74)
Stroke(s) at entry	11	17
TIA(s) at entry	11	20
Stroke and/or TIA at entry		
One hemisphere	4	18
Both hemispheres	4 [a]	2 [a]
Both hemispheres and vbi, syncope or drop attacks	3	3
Neurological signs		
Absent at entry	2	11
Present at entry	9	12

[a] $P < 0.05$ (χ^2 test, Fisher's exact): vbi = vertebrobasilar insufficiency.

Clinical predictors for delayed stroke. An attempt was made to determine which, if any, clinical characteristics predicted recurrent stroke since the identification of a high risk group might have therapeutic implications. In Table 7, the 34 patients are subdivided into two groups on the basis of whether or not recurrent stroke occurred during the follow-up period. The clinical features at presentation are tabulated. The two groups cannot be differentiated on the basis of age or the incidence of stroke and/or TIA at presentation. However, symptoms of cerebral ischaemia were restricted to one hemisphere in 18 of the 23 patients who did not suffer recurrent stroke, whereas bilateral or unilateral hemisphere plus nonhemisphere involvement, was apparent in 7 of the 11 patients who developed a delayed stroke. This difference is significant ($P < 0.05$, χ^2 test, Fisher's exact). Neurological signs were often associated with recurrent stroke during the follow-up period, but differences in the incidence of signs between the two groups did not achieve statistical significance.

Functional outcome. Twenty-four (71%) of the original 34 subjects survived for a mean period of 52 months (range 32–77). At the end of this period, 2 subjects had a degree of mental impairment which was related to recurrent stroke in 1 case and the combination of a single infarct plus diffuse cortical atrophy in the second. Seventeen (50%) could manage their shopping with either no or minimal assistance. Six subjects were still in regular employment, 4 had retired, and the remaining 14 patients had not been working at entry into the study.

DISCUSSION

The eligibility criteria for entry into the EC/IC Bypass Study (1985*a*) precluded patients who had been severely damaged by previous stroke and the present study cannot therefore be regarded as a description of the presentation and outcome of BCAO in general. It does, however, provide insight into the natural history of BCAO in those patients in whom angiography might well be performed and hence diagnosis established during life; it is in this group that such information is of particular importance.

BCAO and Risk Factors

Neither the sex nor the smoking habits (in older subjects) of the individual emerged as independent risk factors for cerebral infarction in the Framingham Survey (Kannel and Wolf, 1983), but the present study suggests that both are important in the aetiology of severe extracranial occlusive vascular disease. The ratio of men to women in the present study was almost 8:1 and 69 out of the total group of 74 patients were heavy smokers throughout most of their adult lives although 6 had been persuaded to give up when they developed the first symptoms of vascular disease. The prevalence of smoking was considerably higher than would be predicted from surveys of the normal population; for instance, 41% of adult male white Americans were smokers in 1983 (United States. Public Health Service, 1984) and in the UK in 1980, 44% of men between the ages of 50 and 59 years were regular smokers (Office of Population Censuses and Surveys, 1985). Studies more limited in scope than the Framingham survey have suggested that smoking is a major risk factor for the progression of stenotic carotid artery lesions (Roederer *et al.*, 1984) and that it is significantly associated with the extent of extracranial vascular pathology, a relationship which is independent of age and other risk factors (Candelise *et al.*, 1984). Of the 1377 patients entered into the EC/IC Bypass Study (1985*a*) in which the majority of patients had unilateral internal carotid occlusion, 82% were or had been cigarette smokers. Patients with unilateral or bilateral carotid occlusion are not typical of the stroke-prone population at large and all the available evidence suggests that smoking is an important aetiological factor in this subgroup.

Presenting Symptomatology of a Haemodynamic Nature

The percentage of patients with unilateral internal carotid artery occlusion who describe classical hemisphere TIAs with an obvious haemodynamic basis is small (Barnett, 1978) and was not reported by any of the 74 patients at entry into the present study. However, 10 subjects could be identified in whom haemodynamic factors may have been responsible for recurrent nonhemisphere symptoms.

A haemodynamic aetiology seems probable because of the orthostatic trigger and the absence of vertebrobasilar pathology in 5 out of the 6 cases evaluated by angiography. No physiological parameters were recorded, but other observers have noted that these symptoms correlate with a posturally-induced fall in retinal artery pressure (Sundt *et al.*, 1976; Stark and Wodak, 1983), and they may also be induced by over-enthusiastic treatment of hypertension (Bogousslavsky and Regli, 1985). In the present study, their presence did not, by itself, distinguish between good and poor outcome. What did emerge was that those patients presenting with bilateral or unilateral hemisphere plus nonhemisphere symptoms fared substantially less well than those whose symptoms were confined to one hemisphere.

One of the 10 subjects with nonhemisphere symptomatology also suffered recurrent visual obscurations and had signs characteristic of chronic ocular ischaemia. These comprised venous engorgement and peripheral retinal haemorrhages and microaneurysms. Although uncommon, it is a characteristic finding in the context of severe obstructive vascular disease and results from the fall in retinal artery pressure secondary to the drop in pressure in the terminal internal carotid artery (Kearns and Hollenhorst, 1963; Ross Russell and Page, 1983).

Symptoms suggestive of haemodynamic disturbance did not necessarily continue during the follow-up period and they rapidly abated in 4 subjects. Presumably this occurs when endogenous collaterals enlarge. An alternative explanation would be the gradual adaptation of the autoregulatory mechanism serving to maintain cerebral blood flow at low perfusion pressures. Whatever the mechanism, the report of 4 patients with severe occlusive cerebrovascular disease by Caplan and Sergay (1976) suggests that these adaptations can occur. Each of their cases developed disabling symptoms of brainstem and hemisphere ischaemia on sitting up after an acute cerebral insult had led to their hospital admission. Systemic blood pressure did not fall appreciably and the paroxysmal symptoms remitted spontaneously within a week or two.

Less Common Symptoms in Patients with BCAO

Seizures. Only 4% of patients in the present series suffered recurrent seizures, which is no higher than expected in a group most of whom have had a stroke (Dodge *et al.*, 1954). We were unable to confirm the suggestion that patients with occlusive carotid disease are particularly prone to develop seizures (Wortzman *et al.*, 1968; Cocito *et al.*, 1982).

Limb shaking. Recurrent transient episodes of limb shaking precipitated by standing were a feature in 2 patients. The attacks were unilateral and affected the arms in both cases. They were not witnessed but the patients' accounts served to distinguish them from jacksonian epilepsy. The onset was sudden and progression was not a feature. Both patients referred to the disturbance as an uncontrollable coarse jerking of the entire limb, precipitated by standing and lasting between one or two minutes. Anticonvulsant drugs proved ineffective.

Episodic dyskinesias have been described as a manifestation of transient cerebral ischaemia (Margolin and Marsden, 1982; Stark, 1985), possibly occurring when blood flow to the basal ganglia is compromised (Yanagihara and Klass, 1981; Baquis *et al.*, 1985). One of the patients reported by Ross Russell and Page (1983) suffered dyskinetic episodes, sometimes associated with visual loss suggesting a haemodynamic mechanism.

Mentation. Mentation was described as impaired in 12% of the patients at presentation, but the entry requirements for the study precluded subjects with severe cognitive dysfunction. The follow-up data demonstrate, however, that cognitive function does not inevitably decline in patients with BCAO. When mild mental impairment was recognized, CT showed infarcts rather than diffuse atrophy, confirming Fisher's view that carotid occlusion, when it causes dementia, does so on the basis of infarction (Fisher, 1968).

Prospective Follow-up

Discrepancies in presentation and outcome almost certainly reflect a bias implicit within the method of case selection. Data, such as those of Fisher (1954), collected from autopsy findings, allude to poor prognosis; angiographically-defined patients do rather better and individual cases (Doniger, 1963; Vitek *et al.*, 1972) are reported because their outcome is so much at variance with conventional teaching. An essential prerequisite for entry into the present study was the absence of a severe neurological deficit and this may favour the selection of patients with good endogenous collaterals and hence reasonable expectations. More than half the patients suffered no further neurological deterioration over a period of almost four years following diagnosis, a quarter died as a result of stroke or unrelated cause and the remainder suffered a recurrent stroke but survived. The figures are rather better than predictions based on data from the four previous studies where patients were diagnosed by angiography (Fields *et al.*, 1961; Hardy *et al.*, 1962; Wortzman *et al.*, 1968; Waltimo and Fogelhom, 1975), which suggested that over a third will be dead within months of diagnosis, a quarter rapidly deteriorate and the remainder remain reasonably intact.

Mechanism of Delayed Ischaemic Symptoms

Orthostatic triggering was historically important in only 1 of the 8 patients with delayed TIAs affecting the hemisphere and/or retina, but was a factor in all 3 patients with recurrent nonhemisphere episodes. Haemodynamic factors did not appear historically important in any of the patients who suffered a delayed stroke but cannot be excluded in the absence of more detailed physiological assessment. Sundt and Whisnant are of the opinion that ischaemic symptoms in the region of an occluded artery are usually haemodynamic in origin (Sundt *et al.*, 1985; Whisnant *et al.*, 1985) and therefore an indication for surgery. Some patients undoubtedly have symptoms which suggest compromised perfusion (Sundt *et al.*, 1976; Ross Russell and Page, 1983; Stark and Wodak, 1983), but haemodynamic insufficiency is not the only explanation for delayed ischaemic episodes and may not be the usual one.

Barnett (1978) drew attention to the external and common carotid arteries in the pathogenesis of delayed ischaemic events involving the hemisphere after proven occlusion of the internal carotid artery. He described 27 examples of postocclusion ischaemia in which haemodynamic factors seemed historically important in only 2 instances. Potential sources of emboli were demonstrated angiographically in the ipsilateral 'alternative circulation' most commonly in the proximal external carotid artery. Thrombus within the proximal stump of the occluded internal carotid artery may also act as a source of emboli to hemisphere or retina (Barnett, 1976; Barnett *et al.*, 1978, 1984) and in 2 cases of recurrent amaurosis fugax, cholesterol emboli were evident funduscopically. Countee *et al.* (1981) reported recurrent retinal ischaemia beyond a cervical carotid occlusion in 17 patients, all of whom had retrograde ophthalmic artery flow. The proximal external carotid artery was either stenotic or ulcerated, or there was an adjacent residual internal carotid stump and retinal branch emboli were evident in 9 patients. External carotid endarterectomy (with excision of the 'stump') appeared symptomatically effective in 10 out of 11 cases, and 6 responded favourably to oral anticoagulants. In the present study, the incidence of external carotid artery disease was higher in patients suffering delayed ischaemic events than in those who did not, but the difference did not reach statistical significance, perhaps because of the small numbers involved.

Various techniques designed to assess the haemodynamic reserve have been described but were not employed in the present study. Orthostatic changes in retinal artery pressure (Sundt *et al.*, 1976; Stark and Wodak, 1983), changes in cerebral blood flow in response to CO_2 challenge (Norrving *et al.*, 1982) and more recently tomographic positron estimates of oxygen extraction ratios and blood volume (Baron *et al.*, 1981; Gibbs *et al.*, 1984; Samson *et al.*, 1985) offer the possibility of delineating those patients in whom collateral reserve is inadequate. There are theoretical attractions for bypass surgery in that subgroup. The present study, however, suggests that haemodynamically induced ischaemic episodes are unusual even in patients with bilateral occlusion of the carotid arteries. Furthermore, none of the 5 subjects with haemodynamic episodes who were treated conservatively suffered a recurrent stroke so these symptoms did not emerge as an indicator of poor prognosis. The results of the EC/IC Bypass Study (1985*b*) are now available and it is clear that surgery does not benefit patients with BCAO. Indeed, it may be that patients with haemodynamic compromise are at particular risk of stroke during surgery and further analysis of the comparison between conservative and surgical management will be the subject of a subsequent publication.

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A MORPHOMETRIC STUDY ON SURAL NERVES IN METACHROMATIC LEUCODYSTROPHY

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SUMMARY

This study reexamines peripheral neuropathy in infantile, juvenile and adult metachromatic leucodystrophy. A computer-assisted method was used which gives more detailed information on abnormal fibre structure from scatter diagrams of the g ratio (axon diameter/fibre diameter). The data show marked and statistically significant reductions in sheath thickness, particularly for the thick myelinated fibres, and most severe in the juvenile and adult forms. This is interpreted as evidence of remodelling of virtually the entire fibre population, without a clear-cut selectivity for either thin or thick fibres.

INTRODUCTION

Arylsulphatase A deficiency resulting in metachromatic leucodystrophy (MLD) mainly affects the myelin sheaths of the central and the peripheral nervous system. This progressive disease is marked by breakdown of myelin sheaths and, subsequently, of axons. Metachromatic material is found within the lysosomes of Schwann and other cells both in the peripheral and central nervous system. Deposits of metachromatic material in peripheral nerves are significant for the clinical diagnosis of MLD.

The genetically determined autosomal recessive disease manifests at all ages. There are three main forms of MLD: late infantile (onset between 12 and 30 months), juvenile (onset between 3 and 10 years) and adult. The disease involves peripheral nerves, and its first manifestation may be in terms of a peripheral neuropathy. There is microscopic evidence of segmental demyelination and small onion-bulb formations, suggesting concurrent widespread remyelination (Dayan, 1967; De Silva and Pearce, 1973; Meier and Bischoff, 1976; Thomas *et al.*, 1977; Luijten *et al.*, 1978; Martin *et al.*, 1982).

Morphometric analyses of peripheral nerves by Martin and Joris (1973) and Martin *et al.* (1982) were based on the customary approach using histograms

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showing loss of nerve fibres of specified calibre classes. The present study re-examines peripheral neuropathy in the three types of MLD using a computer-assisted method which gives additional information on relative myelin sheath thickness from scatter diagrams of the g ratio (axon diameter/fibre diameter). The data obtained show that most fibres have abnormally thin sheaths, indicating extensive remodelling of the entire fibre population.

MATERIAL AND METHODS

Sural nerve biopsies were obtained from 9 patients with MLD: 4 with the late infantile form, 2 with the juvenile form and 3 with the adult form. Patients without pathological changes were used as age-matched controls. Biopsies were fixed immediately in buffered glutaraldehyde for 3–4 h, washed in the same buffer and dehydrated in increasing concentrations of ethanol. Tissues were embedded in Araldite via 2-4-epoxypropane. Thin sections were cut, mounted on 400-mesh copper grids and stained with uranyl acetate and lead citrate.

Morphometry was performed on electron micrographs using the method described in detail by Friede and Beuche (1985*a*). Briefly, the entire profile of the nerve was examined with electron micrographs taken of every grid opening at a magnification of 3400 × with a Zeiss EM10 electron microscope. The inner and outer surfaces of the sheaths were traced manually with a cursor and measured with a Kontron Videoplan. The computer program calculates, along with many other options, the noncircularity of fibres (area axoplasm/area of a circle having the same circumference), the area and the diameter of the circular axon profile, and the relative sheath thickness expressed by the g ratio (axon diameter/fibre diameter). Scatter diagrams showing the g ratio versus circular axon diameter and the thickness of the myelin sheaths versus axon diameter were printed for control and pathological nerves. In several previous studies it was found to be most informative to base data on the diameter of the circular axon profile rather than axon area. This eliminates the variation in fibre profile caused by noncircularity from in vivo osmolar variation and, particularly, by tissue processing. Such irregular shrinkage affects axon area, but not circular axon diameter.

RESULTS

In all patients, the diagnosis of MLD was based on metachromatic material detected by light and electron microscopy, and biochemically through decreased leucocyte arylsulphatase A activity. Light and electron microscopy findings were consistent with previous reports (Meier and Bischoff, 1976; Thomas *et al.*, 1977; Bosch and Hart, 1978; Luijten *et al.*, 1978; Hahn *et al.*, 1982; Martin *et al.*, 1982). There was evidence of demyelination, with myelin breakdown products and debris-laden endoneurial macrophages. Sections stained with acidic cresyl violet showed brown metachromatic deposits in macrophages and Schwann cells. Semithin sections revealed loss of myelinated fibres, this being most severe in the adult form, with considerable variation between patients. Many remyelinated fibres of large calibre with thin myelin sheaths were present (fig. 1).

Electron microscopy revealed various types of inclusions. Macrophages and Schwann cells contained prismatic inclusions (fig. 2), tuffstone, zebra bodies and vacuoles (Grégoire *et al.*, 1966; Bischoff and Ulrich, 1967; Thomas *et al.*, 1977). Occasional inclusions were encountered within axons.

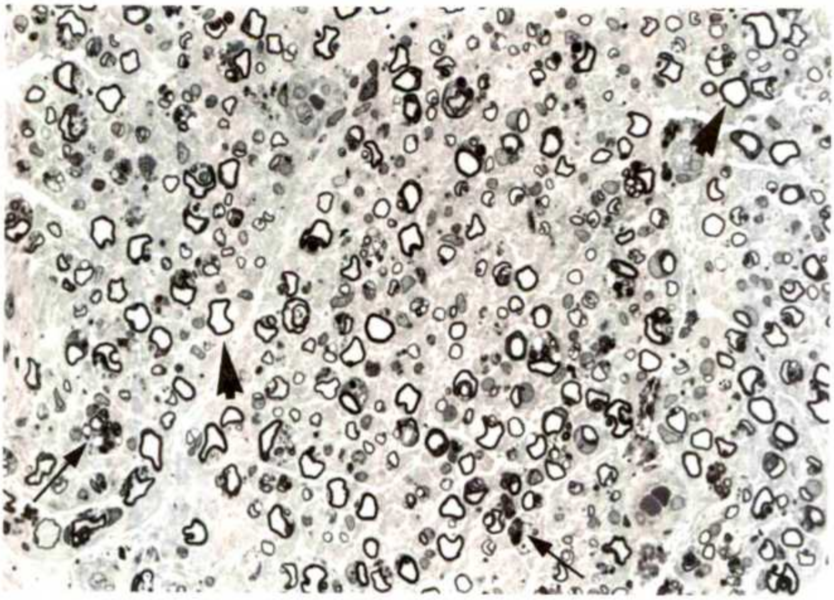

FIG. 1. Semithin section of the sural nerve of a patient with the juvenile form of MLD showing remyelinating fibres (arrowheads) and macrophages filled with fragments of myelin and granular material (thin arrows). Toluidine blue, ×430.

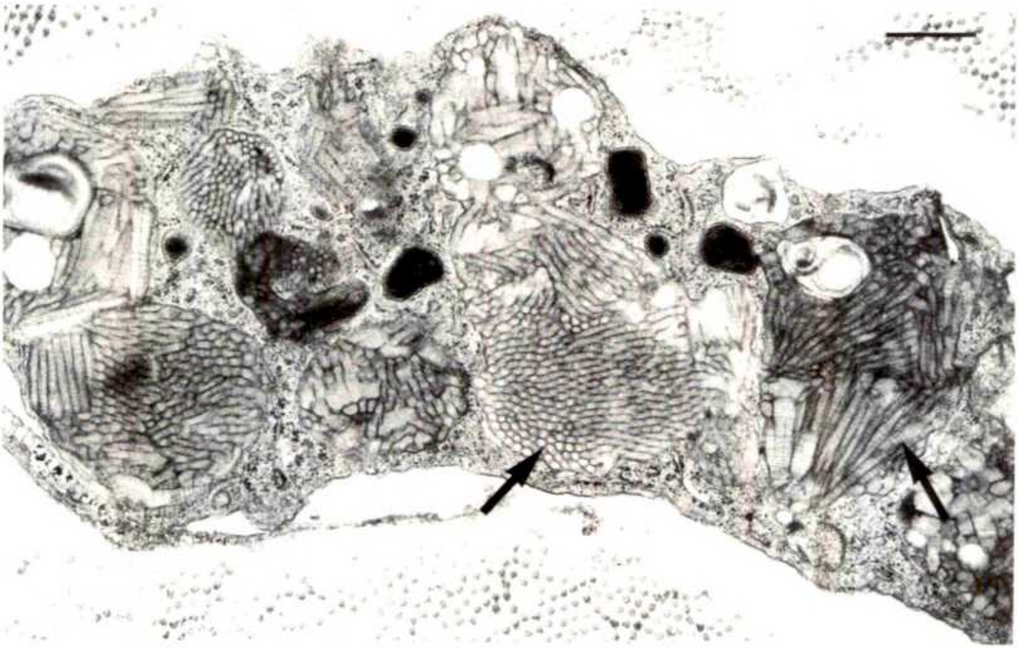

FIG. 2. A process of a macrophage containing prismatic inclusions (arrows). Inclusions are cut at different angles. Bar = 0.5 μm.

TABLE. MORPHOMETRIC DATA OF SURAL NERVES IN LATE INFANTILE, JUVENILE AND ADULT METACHROMATIC LEUCODYSTROPHY AND AGE-MATCHED CONTROLS (MEAN ± SD)

	Late infantile MLD ($n = 4$)	*Controls* ($n = 3$)	*Juvenile MLD* ($n = 2$)	*Controls* ($n = 3$)	*Adult MLD* ($n = 3$)	*Controls* ($n = 4$)
g ratio						
Total population	0.85±0.06	0.78±0.05	0.82±0.06	0.74±0.08	0.77±0.07	0.73±0.08
No. of fibres measured						
Axon diameter < 5 μm	517	640	435	549	259	604
Axon diameter 5–12 μm	220	250	169	257	128	246
g ratio						
Axon diameter < 5 μm	0.85±0.06	0.79±0.05	0.81±0.05	0.76±0.07	0.77±0.07	0.74±0.08
g ratio						
Axon diameter 5–12 μm	0.85±0.06	0.75±0.05	0.84±0.06	0.70±0.09	0.77±0.06	0.68±0.07
Mean axon diameter, circular						
Total population (μm)	4.33±1.79	4.25±1.71	3.95±1.64	4.55±1.81	4.55±1.46	4.57±1.99
Axon diameter, circular						
< 5 μm	3.37±0.88	3.33±0.74	3.06±0.77	3.50±0.79	3.70±0.79	3.49±0.76
Axon diameter, circular						
5–12 μm	6.60±1.26	6.63±1.08	6.11±0.97	6.78±1.28	6.25±0.93	7.24±1.46
Noncircularity factor						
Total population	0.63	0.65	0.52	0.63	0.58	0.59
Noncircularity factor						
Axon diameter < 5 μm	0.63	0.64	0.48	0.63	0.56	0.57
Noncircularity factor						
Axon diameter 5–12 μm	0.63	0.69	0.58	0.61	0.64	0.66
Percentage of fibres						
Axon diameter < 5/5–12 μm	70/30	72/28	72/28	68/32	67/33	71/29

The means are for the pooled measurement obtained from all the patients in a given class. No SDs are given for noncircularity factors because of the asymmetric nongaussian distribution of values.

Morphometric Analysis

The quantitative data for myelinated sural nerve fibres in MLD and control patients are summarized in the Table.

In the scatter diagrams shown in figs 3, 4, 5 we superimposed the data from all the patients in each group: for the late infantile form the scatter diagrams are for 3 patients with a total of 737 fibres measured, and 3 controls (n = 890); there were 2 juvenile patients (n = 604) with 3 controls (n = 806); and 3 adult patients (n = 387) with 4 controls (n = 850).

Fascicular area was measured with the Videoplan, and the total number of myelinated fibres was counted. Fibre densities (fibres/mm^2) were 8500 for a late infantile control, 9300 for a juvenile and 7400 for an adult control. Fibre densities for the late infantile patients were 5800, 8100, 8100 and 5700; for the juvenile patients 7100 and 10 000; for the adults 3600, 6200 and 2700. The loss of myelinated fibres, accordingly, was relatively mild in the late infantile and juvenile patients, whereas 2 of the 3 adult patients had lost more than half of their myelinated fibres.

Late Infantile MLD

Nerve fibres generally had thinner myelin sheaths in patients with MLD than in control nerves (fig. 3E, F). This was also shown by measurements of relative sheath thickness (g ratio) which gave higher means for the MLD patients than for controls (MLD: 0.85; control: 0.78) (fig. 3A, B). Such mean values for the entire fibre population are of limited significance, however, because normal sural nerves show two distinct fibre populations (Friede and Beuche, 1985*b*). One population is formed mostly by fibres below 5 μm axon diameter and has relatively thin myelin sheaths. The other is formed by fibres of 5 to 12 μm axon diameter and has thicker myelin sheaths which, in addition, show an increase in the g ratio with fibre calibre. These two populations are evident in all three normal control groups, and their separation becomes more distinct with age, in agreement with previous observations (figs 3B, 4B, 5B). It is necessary, therefore, to analyse the populations of thin and thick fibres separately to determine whether there is preferential damage to either group, and also whether sheath thickness is reduced in both populations.

The demarcation of two fibre classes (axon diameter less than 5 μm; thin sheaths; axon diameter between 5 and 12 μm; thick sheaths) found in controls (fig. 3B) was less distinct in the MLD nerves (fig. 3A). The g ratios of both groups of fibres were increased and had the same mean value (0.85) (fig. 6). The control nerves, in contrast, had lower g ratios and the two classes differed from each other (thin fibres: 0.79; thick fibres: 0.75) (fig. 6). The difference in relative sheath thickness between MLD nerves and controls was highly significant ($P < 0{\cdot}01$) for both thick and thin fibres (Student's t test.)

There were no differences in the noncircularity factors between the MLD nerves and controls, nor were there differences between the thick and thin fibres. There

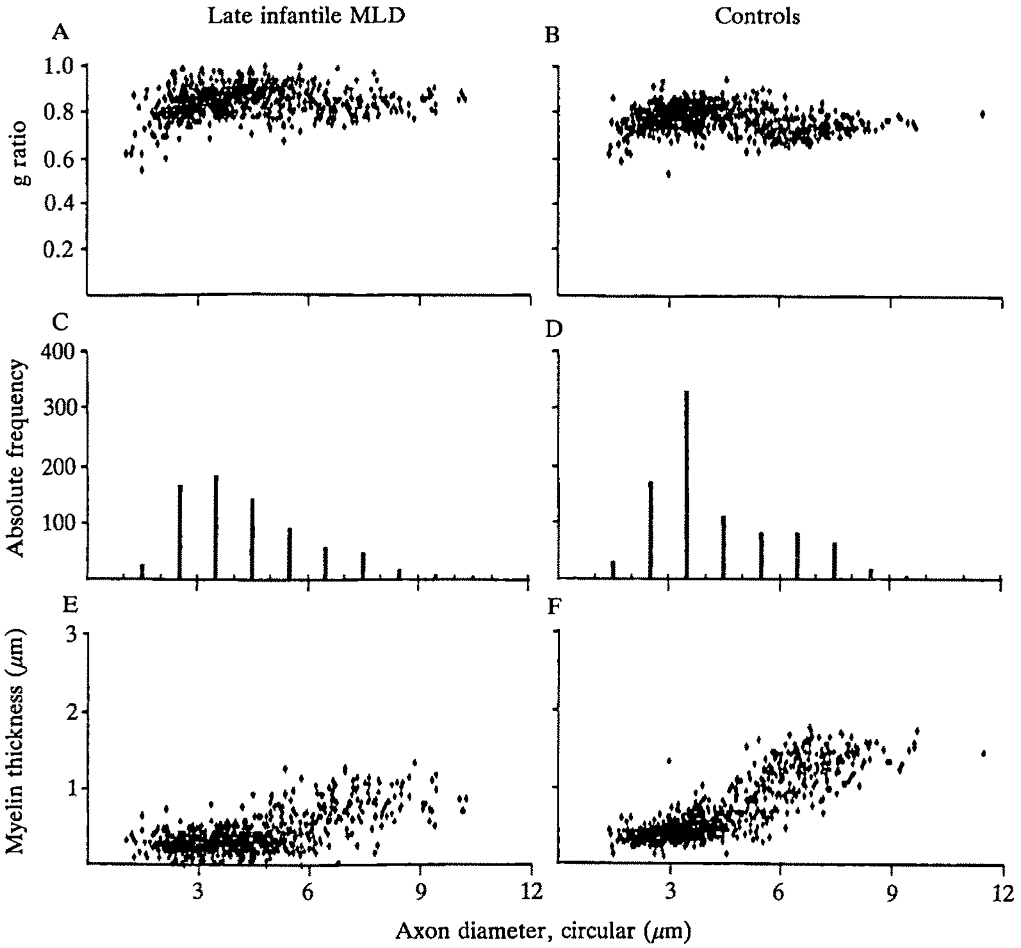

FIG. 3 Scatter diagrams of g ratio and absolute frequencies of sural nerve fibres in a late infantile MLD (A) compared with normal controls (B). The separation of the two populations of fibres seen in the control nerve (B) is less distinct in the MLD patients (A). Also the fibres have significantly higher g ratios than those of the control. If myelin thickness is plotted against axon calibre, the slope is lower for MLD nerves (E) than for controls (F). The fibres with axon diameters between 5 and 12 μm, in particular, have distinctly thinner myelin sheaths than the controls.

was no evidence of selective loss of either thick or thin fibres (fig. 3C, D): the quotient of the two populations was 70/30 in MLD nerves and 72/28 in controls. Also, mean axon calibre did not differ (*see* Table).

Juvenile MLD

The myelin sheaths, particularly of axons in the range of 5 to 12 μm, were markedly thinner in MLD nerves (fig. 4E) than in the controls (fig. 4F). The mean g ratio of the entire MLD fibre population (fig. 4A) was higher (0.82) than in the control nerves (0.74; figs 4B, 6).

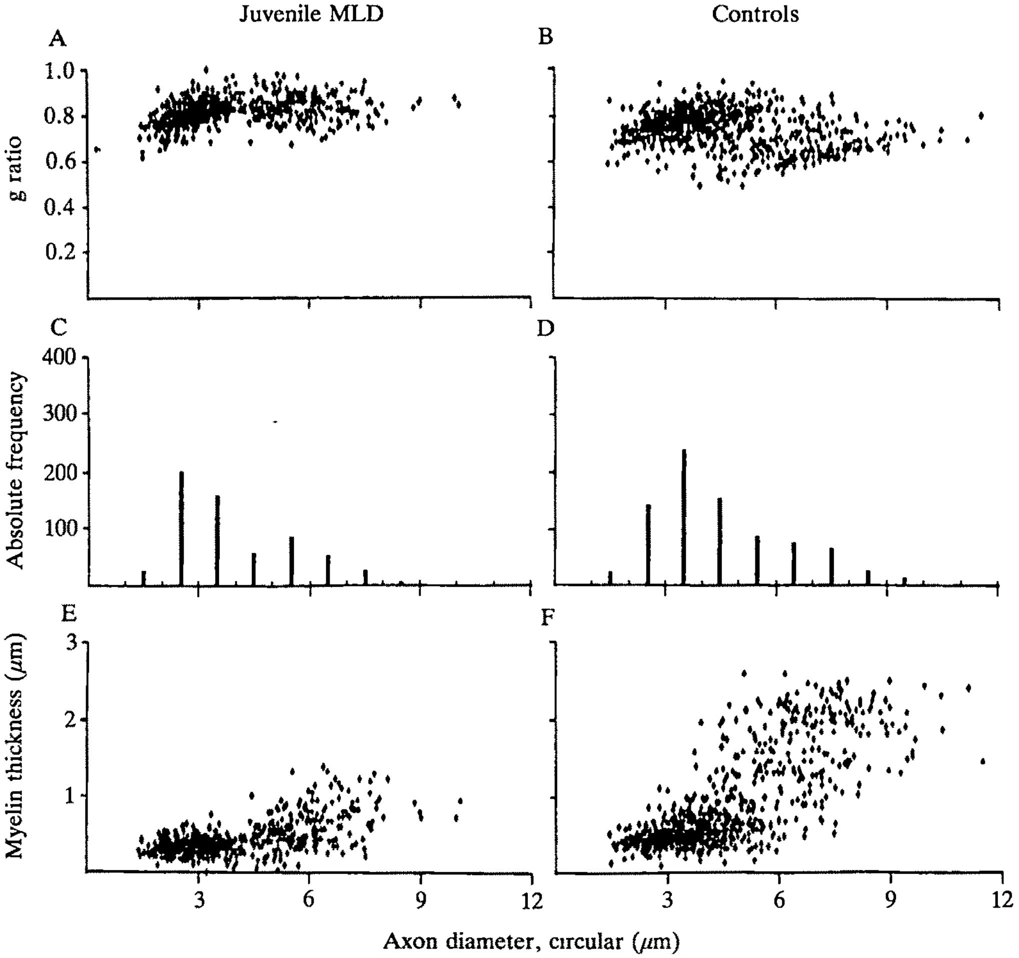

FIG. 4. Scatter diagrams of g ratio and absolute frequencies of sural nerve fibres in juvenile MLD (A); fibres generally have a higher g ratio than the control (B). This is particularly obvious for the fibres with an axon diameter between 5 and 12 μm, but also is seen for thin fibres. The curves E (MLD) and F (controls) confirm that MLD nerves have much thinner myelin sheaths than the controls.

In the control nerves there was a clearer separation of the two fibre classes than was found at younger ages (compare fig. 4B with 3B). In the MLD nerves, sheath thickness was more reduced in thick than in thin axons (fig. 4E, F). Thick fibres thus had a higher g ratio (0.84) than thin fibres (0.81) in the MLD nerve, whereas the proportion was inverse (0.70 versus 0.76) for controls (figs 4A, 4B, 6). The differences between MLD nerves and controls were highly significant ($P < 0.01$) for both thick and thin fibres. The fibres with an axon diameter below 5 μm were more shrunken, having a slightly smaller (0.48) noncircularity factor than the control fibres (0.63). On inspection of the scatter diagrams, there appeared to be a reduced number of very thick fibres of 8 to 12 μm axon diameter (fig. 4A–D).

However, the relative frequency of the two fibre populations in MLD nerves (72/28) did not differ from the controls (68/32) (*see* Table). We interpret this apparent discrepancy as indicating a slight reduction in the calibre of remyelinated or regenerated fibres but without evidence of selective loss either of thick or thin fibres.

Adult MLD

The g ratio of the entire population of sural nerve fibres was higher in MLD (0.77) than in control nerves (0.73), similar to the late infantile or juvenile forms (figs 5A, 5B, 6). Thick fibres (5–12 μm) had greatly reduced sheath thickness with a g ratio of 0.77 compared to 0.68 for the control nerves, the difference being highly

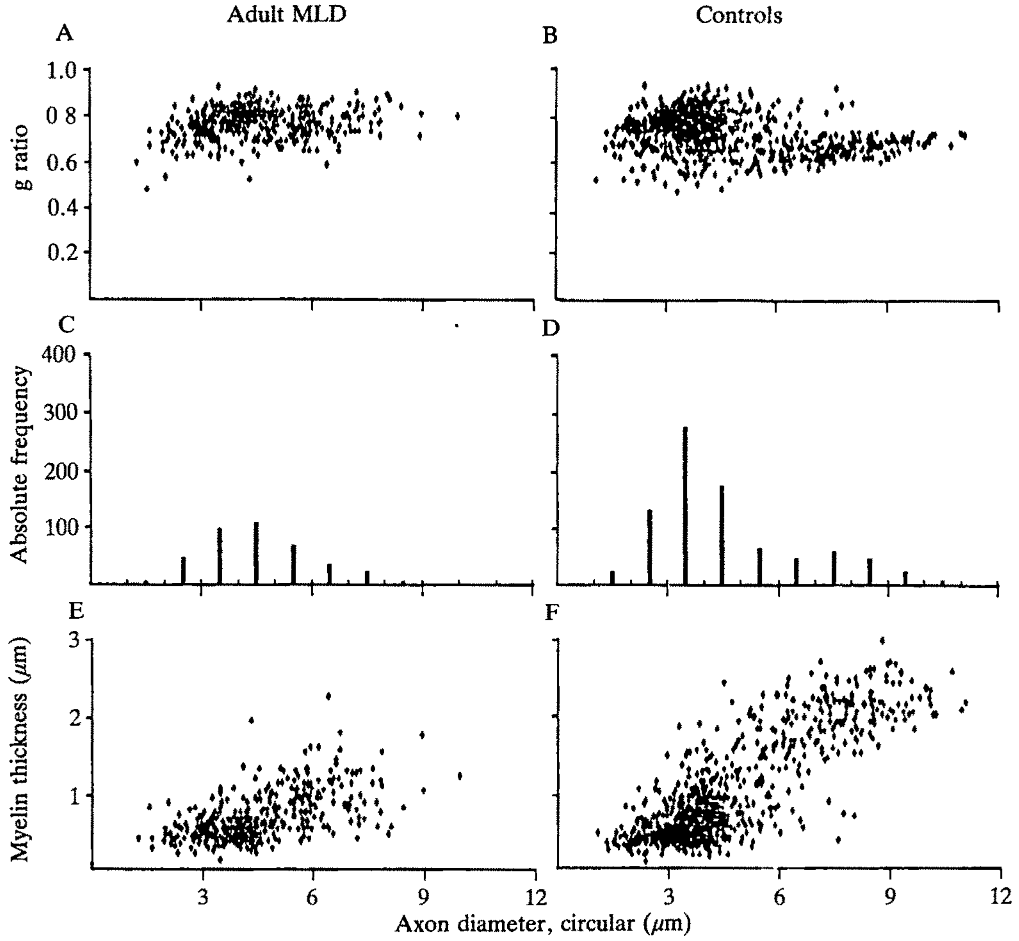

FIG. 5. Scatter diagrams of g ratio and absolute frequencies of nerve fibres in the adult form of MLD. The separation of the two fibre populations seen in the control (B) is obliterated in the MLD nerves (A). Myelin thickness is reduced in MLD (E), particularly for the axons with diameters between 5 and 12 μm, compared with controls (F). There are fewer very thick fibres (D), but the quotient between the two calibre classes is near normal (*see* text).

significant ($P < 0.01$). This was also evident from the measurements of myelin sheath thickness (fig. 5E, F). The fibres of small axon calibre (less than 5 μm) showed a less distinct increase of the g ratio (from 0.74 to 0.77), and the difference was statistically not significant (Table; fig. 6). There were no differences in noncircularity factors. As in the juvenile patients, there were fewer axons thicker than 9 μm (fig. 5C, D). Again, the quotient thick/thin fibres was similar for MLD nerves (67/33) and for controls (71/29), indicating that neither group was damaged selectively even though some reduction in calibre had taken place.

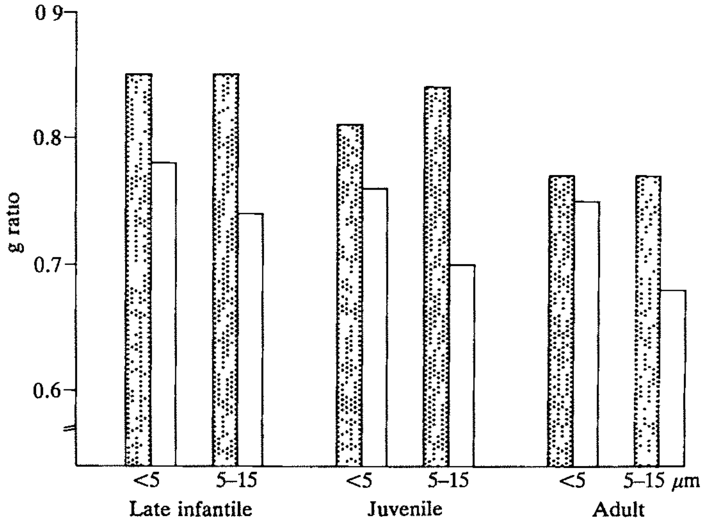

FIG. 6. Histogram of the mean g ratios of fibres of less than 5 μm axon calibre and fibres of 5–12 μm axon calibre in the late infantile, juvenile and adult forms of MLD with age-matched controls. MLD (▨), Controls (□)

DISCUSSION

Each of the 9 patients analysed here had metachromatic leucodystrophy identified by its specific inclusions in the sural nerve and confirmed biochemically by the demonstration of arylsulphatase A deficiency in leucocytes. Previous morphometric studies of peripheral nerves of patients with the different forms of MLD used a customary approach of presenting axon calibre and myelin sheath thickness in the form of histograms (Martin and Joris, 1973; Martin *et al.*, 1982). There was a loss of the normal bimodal distribution of myelin sheath thickness only for the late infantile form of MLD; the juvenile and adult subtypes presented a normal bimodal distribution with a reduction in the number of thickly myelinated fibres.

The morphometric approach used here has several advantages compared with histograms. Measurements made in low power electron micrographs give a precise definition of sheath thickness and its variations, particularly for thin fibres. Automatic correction for circularity eliminated scatter due to axon shrinkage caused by chemical fixation and in vivo or in vitro osmotic factors. Documentation of data in terms of scatter diagrams of relative myelin sheath thickness (the g ratio) gives more information than using either histograms of calibre alone or sheath thickness versus calibre. These scatter diagrams are more effectively interpreted with the knowledge that relatively short internodes have slightly thinner sheaths than internodes of 'normal' length, and vice versa, as observed in isolated fibres (Friede and Bischhausen, 1982) and in growing nerves (Friede *et al.*, 1985). Regenerated or remyelinated fibres with their markedly foreshortened internodes are readily recognized by their thinner sheaths or higher g ratios, respectively (Beuche and Friede, 1985, 1986). Unfortunately, there was no material available for teased fibres in the present (retrospective) study. However, marked foreshortening of internodes in metachromatic leucodystrophy was previously shown by Martin *et al.* (1982).

The myelinated fibres of the normal human sural nerve can be separated, according to age, into two populations, having a characteristic distribution of the g ratio (Friede and Beuche, 1985*b*). A population of fibres of thin calibre is characterized by relatively thin myelin sheaths and a high g ratio. The rest of the fibres of larger calibre show a regression of sheath thickness with fibre calibre. The significance of the normal population of 'high g ratio fibres' is still unknown. Ongoing studies suggest that they may represent a late myelinating fibre population. In nerve regeneration and in experimental neuropathy a new population of fibres with still higher g ratios is formed which could be identified as regenerating or remyelinating fibres (Beuche and Friede, 1985, 1986).

Our morphometric examination of the sural nerves of patients with MLD showed evidence of reduced myelin sheath thickness for both classes of myelinated fibres in all forms of MLD except for the thin fibres in the adult form, where the difference, though noticeable, was not statistically significant. Myelinated fibres had generally higher g ratios than the controls. The fibres with greater axon diameter were more severely affected than fibres with smaller axon diameter. This difference was particularly evident in the juvenile form, in which the proportion of the g ratios of the two fibre populations was reversed in comparison with the control or late infantile and adult subtypes.

Scatter diagrams showed a nearly complete absence of the normal g ratio values of thickly myelinated medium to thick (5–12 μm) fibres, especially in the juvenile and adult forms (figs 4B, 5B). These were replaced by a new population of fibres with thinner myelin sheaths forming a new, higher regression in the scatter diagrams and slightly shifted to the left. This shift to the left indicated some reduction in axon diameter, but the quotient of the number of thick and thin fibres was nearly unchanged. When it is realized that, in addition, 2 of the adult patients had lost more than half of their nerve fibres, they could not possibly have a near normal quotient of thick and thin fibres if one class was damaged selectively. The impression of selective damage to thick fibres, gained from the inspection of calibre histograms, is evidently erroneous. There is no direct evidence, from the scatter diagrams shown here, to indicate whether the reduced sheath thickness resulted from regeneration or from remyelination. Our data document, nonetheless, the existence of an extremely severe and chronic neuropathy which leads—in the course of time—to a complete remodelling of the entire fibre population replacing practically all of the thick myelinated fibres with a new population having abnormally thin myelin sheaths.

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A REASSESSMENT OF THE ACCURACY OF REINNERVATION BY MOTONEURONS FOLLOWING CRUSHING OR FREEZING OF THE SCIATIC OR LUMBAR SPINAL NERVES OF RATS

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SUMMARY

The accuracy of reinnervation in peripheral nerves following second degree injuries, which do not disrupt the longitudinal continuity of the endoneurial sheaths, has been studied in rats. The sciatic nerve or lumbar spinal nerves (that is the extraspinal nerves before their fusion in the sciatic plexus) were crushed with fine watchmakers' forceps in neonatal and adult rats. In addition, the lumbar spinal nerves were frozen in a group of 5 adult rats. After allowing reinnervation to occur for 5 to 9 weeks, the motoneurons whose axons ran in the plantar nerve were labelled retrogradely with horseradish peroxidase. Their positions in the grey matter of the lumbar spinal cord were recorded and compared with those labelled from the contralateral unoperated plantar nerve. Very few errors of projection occurred after a crush lesion of the adult sciatic nerve but all the other lesions produced significant numbers of errors. The order, starting with the preparations with fewest errors was as follows (numbers in brackets = percentage of neurons misplaced): sciatic crush in adult (3%), sciatic crush in neonate (23%), spinal nerve freeze in adult (23%), spinal nerve crush in adult (35%), and spinal nerve crush in neonate (72%). It seems that a significant number of axonal growth cones cross endoneurial sheaths after crush or cryoinjuries. Explanations for the difference in observed reinnervation accuracy between young and old rats and between lesions in peripheral nerves and spinal nerves are discussed. The first is that axons in peripheral nerves in older rats have a less penetrable endoneurial membrane encasing them. The second is that the amount of misrouting is the same at all lesion sites but is much less easily detectable after sciatic lesions than spinal nerve lesions. This is because axons are organized in a 'musculotopic' manner in peripheral nerves and exchange of axon positions will occur largely between axons destined for the same peripheral target. In contrast, exchange of positions of axons in spinal nerves will lead to more overt errors because at this site axons destined for particular muscles do not lie side by side but are intermingled with axons innervating other peripheral targets.

INTRODUCTION

It is well known that the degree of functional recovery after wallerian degeneration of damaged peripheral nerve fibres depends upon whether the connective tissue

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sheaths (endoneurium and/or perineurium) have been disrupted at the time of the injury (*see* Sunderland, 1978). Where the endoneurial sheaths are not damaged (a so-called second degree nerve injury, Sunderland (1951)) it is generally agreed that the recovery of function is nearly perfect. The accuracy of reinnervation needed to achieve such a good functional effect is held to occur because the regrowing nerve fibres are constrained to run along inside the old basal lamina sheaths which make up the inner layer of the endoneurium and are thus led automatically back to the appropriate place (Thomas, 1974). Yet growth cones can readily cross endoneurial sheaths as they do when collateral nodal sprouts are formed within partially denervated muscles (Hoffman, 1950; Brown *et al.*, 1981). They will also cross the basal lamina of dead muscle fibres to grow along inside them (Keynes *et al.*, 1984).

It seemed unlikely to us that either the growth cones or the endoneurial sheaths of spinal and limb nerves were different from those within muscle. Therefore successful recovery of function probably occurs in spite of some exchange between endoneurial sheaths by the regrowing axons. Good recovery could still be achieved in spite of such misrouting, either because a few mistakes would have little functional effect and/or because most of the swapping occurs between axons destined for the same target. We have been able to test this hypothesis using retrogradely transported horseradish peroxidase (HRP) to label the motoneurons whose axons run in the plantar nerves following a crush injury to the sciatic nerve in the midthigh. The results of this procedure have been compared both with the normal projection and with that obtained after crushing or freezing the lumbar spinal nerves, that is, the extraspinal nerves which are the product of fusion of dorsal and ventral nerve roots and which have emerged from the intervertebral foramina but have not yet merged with their neighbouring spinal nerves to form the sciatic plexus. Within the spinal nerves axons destined for particular muscles are not gathered together as they are in the sciatic or other limb nerves (Landmesser, 1984). Any tendency for axons to exchange from one endoneurial sheath to another would be more readily revealed after lesions in the region of the spinal nerves, since neighbouring axons are less likely to be projecting to the same target. We chose crushing with forceps as the main method for producing wallerian degeneration because this technique does not disrupt the longitudinal continuity of the endoneurial sheaths (Haftek and Thomas, 1968). However, this method can bring about some points of fusion between adjacent endoneurial tubes (Haftek and Thomas, 1968). In addition, therefore, in one set of experiments we froze the nerves, a method which is reported not to damage endoneurial sheaths (Carter *et al.*, 1972). This technique does not subject the endoneurial tubes to the sudden expansion by laterally displaced axonal contents which leads to the points of rupture and cross-linking seen after crushing.

The results from the sciatic and spinal nerves differ in the predicted way, with many errors being detected after spinal nerve lesions, unequivocally demonstrating that axons regrowing after even minimal nerve trauma can interchange endoneurial sheaths. The errors are greater when the lesions are made in neonatal rats which may be because escape from newly formed endoneurial sheaths occurs more easily.

METHODS

Material

Two age groups of rats were used for initial nerve lesions: 10 days and 6–8 wks. The neonatal rats were anaesthetized with ether, the adult rats with intraperitoneal chloral hydrate (3.5% chloral hydrate, 1 ml/100 g bodyweight). Either the sciatic nerve was exposed in the left thigh or the left lumbar spinal nerves 4, 5 and 6 were exposed via laparotomy and retraction of the psoas and iliacus muscles.

Lesioning

We used two methods to produce nerve degeneration both of which are believed not to disrupt the longitudinal continuity of the endoneurial sheaths. The first was simply to crush the nerves for approximately 20 s at a single point with the tips of a no. 5 Swiss watchmakers' forceps and then to apply a second 1 s squeeze proximally to check that no movement occurred. The sciatic nerve was crushed in the midthigh region. Each lumbar spinal nerve was crushed individually. Electron microscopy has shown that such crush lesions do not transect the endoneurial sheaths (Haftek and Thomas, 1968) but they do lead to complete paralysis and degeneration distal to the lesion. The second method, which was used to confirm the findings of the crush lesions, was to freeze the exposed lumbar spinal nerves 4, 5 and 6 of adult rats with solid carbon dioxide for approximately 2 min. Roughly 3 mm of nerve froze with this treatment and on thawing there was no sign of any mechanical damage to the nerves. Such cryolesions are also reported to cause no endoneurial damage (Carter *et al.*, 1972). In all the rats, whether neonate or adult, crushed or frozen, there was complete paralysis of the lower leg and foot. Movement began to return after about 2 wks for the sciatic and about 4 wks after spinal nerve surgery

Labelling of Motoneurons Projecting down the Plantar Nerves

Five to 7 wks after sciatic lesions and 6 to 9 wks after root surgery the rats, now of course all adult, were reanaesthetized with chloral hydrate and the right (control) and left (experimental) plantar nerves exposed at the ankle. The proximal end of the medial plantar nerve was sucked into a tightly fitting pipette containing 30% HRP (Sigma type VI) in 0.9% saline and 2% lysolecithin (Sigma type I), so that the cut ends came into contact with this solution. Contact was maintained for approximately 30 min. In some cases this required reapplication of the suction pipette after removal of small accumulations of blood at the nerve end.

After 48 h the rats were again deeply anaesthetized and perfused intracardially with heparin saline (800 units/l) at room temperature until the liver was uniformly pale, followed by a solution of 1.25% glutaraldehyde and 1% paraformaldehyde in 0.1 M phosphate buffer, pH 7.4 for 30 min.

The lumbar spinal cord was removed and placed in 30% sucrose in 0.1 M phosphate buffer (pH 7.4) overnight at 4 °C. Serial transverse sections at 100 μm were cut on a freezing microtome, mounted on subbed slides and reacted with tetramethylbenzidine (TMB) according to the method of Mesulam (1982).

Analysis of Data

Positions of all labelled motoneurons in each section were recorded automatically by projecting the image of the spinal cord onto a digitizing tablet connected to the serial port of a microcomputer. For each section the coordinates of the grey matter of the cord were first recorded by placing the cursor on the most lateral margin of the grey matter, the central canal and the tip of the ventral horn. The position of each labelled cell relative to these landmarks was automatically calculated and stored by the computer as the cursor was placed over each cell. The position of each cell in the long axis of the cord was known from the section in which it occurred. Sections from different animals were aligned in the longitudinal axis by labelling the most caudal section which contained labelled neurons as 100 and counting sections forward from that point. The normal plantar pool is 3 mm long (Nicolopoulos-Stournaras and Iles, 1983) and virtually all plantar neurons in normal rats (top row in fig. 2) were therefore in sections 70 to 100 (30 sections of 100 μm each). The vertical position of each cell was normalized by expressing it as a percentage of the distance from the tip of the ventral horn to the central canal (y/Y in fig. 1) and its horizontal location was normalized by expressing it as a percentage of the distance from the lateral margin of the grey matter to the central canal (x/X in fig. 1). In displaying the data we have deliberately overexpanded the horizontal axis of the left-hand scattergrams of figs 2 and 3 by a factor of 1.5 times so that individual points would not become too obscured. Similarly in the right-hand scattergrams which plot the vertical position of each cell against the section in which it appeared, we have overexpanded the vertical axis by a factor of about 3.6 times compared with the horizontal for the same reason. The vertical axes in the right and left scattergrams are the same.

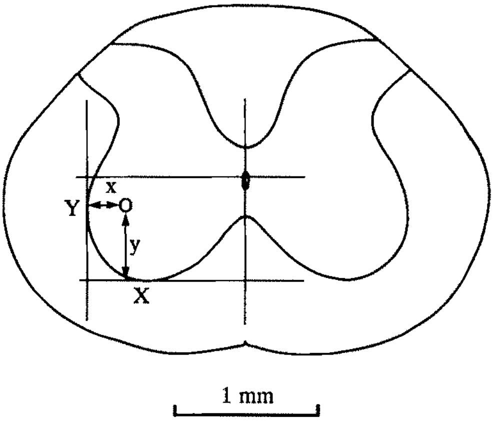

FIG. 1. Diagram of rat lumbar spinal cord to show method of recording the vertical and horizontal positions of labelled motoneurons (*see* Methods for further details).

The mean positions of the labelled cells in all 3 axes in control and experimental groups were compared statistically using Student's t test. We compared not only the pooled data for each group of experiments against the pooled control data but also in each experiment compared the experimental and control sides of each rat (except in 2 cases detailed in the Results section).

RESULTS

The plantar nerve was chosen for these experiments as the motoneurons whose axons normally run in it lie in a very characteristic rather circumscribed location in the dorsolateral grey matter of the ventral horn (Nicolopoulos-Stournaras and Iles, 1983). This can also be seen from the top two scattergrams in fig. 2 which display the location of 900 plantar motoneurons from the control side of 23 of the experimental rats, in transverse section on the left, and from a side view on the right; 99% of the cells lie in a 3 mm long column between our vertical coordinates 74% and 149% and horizontal coordinates 0.5% and 30%. Note that in the top

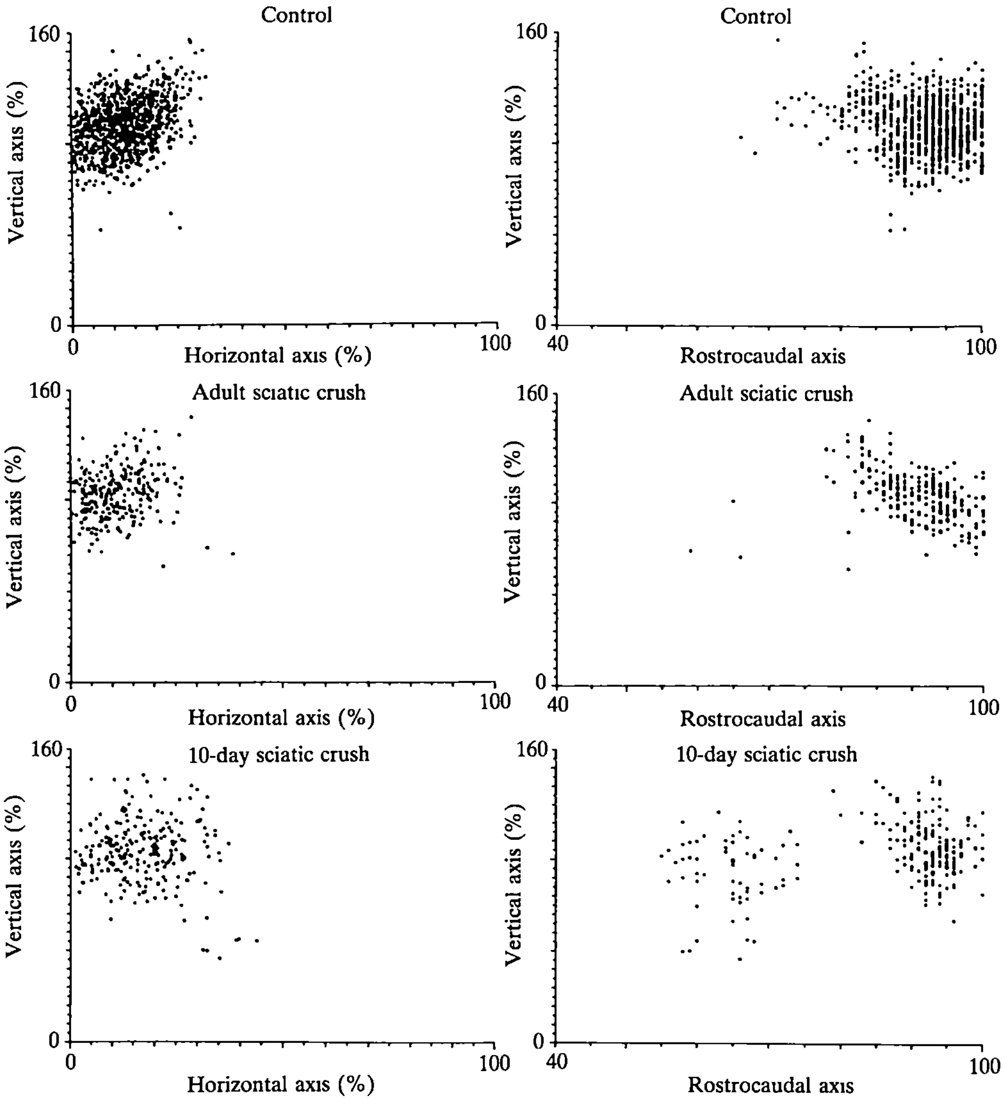

FIG. 2. Scatter diagrams giving the normalized positions of all retrogradely labelled motoneurons. These are shown in the transverse plane on the left, and in the longitudinal axis viewed from the side on the right. Results from 3 different situations are displayed. *Top panels*, results from 23 controls; *middle pair*, results from 5 rats after left sciatic nerve crush in the adult; *bottom pair*, results from 5 rats whose left sciatic nerve was crushed when they were 10 days old (*see* Methods for details of display format). In the plots in the left-hand panels the horizontal axis is expanded by a factor of 1.5 times, and those on the right, the vertical axis is expanded relative to the horizontal by 3.6 times.

two histograms of fig. 2 we have combined the control data from all rats, both those operated on as neonates and those operated on as adults. This seemed logical as all the rats were adult when the motoneurons were retrogradely labelled, and there was no reason to suppose that the normal plantar pool systematically varied in a major way between different litters. In the sections below, describing the results from different lesions, individual comparisons of right (control) and experimental (left) sides are made. In 2 of the 25 rats, cells on the control side unfortunately did not label and comparisons of the individual data from these experiments have been made with the pooled control data of the appropriate experimental group.

TABLE 1 SUMMARY OF EXPERIMENTAL RESULTS

Experiment	*No of rats*	*Regeneration time (wks)*	*Total no. of cells labelled*	*Mean no of cells labelled per experiment ±SE*	*No of abnormal cells (i.e. outside 99% limits)*	*% abnormal cells*
Right side controls	23	—	900	39.1 ± 6.24	9	1%
Adult sciatic crush	5	5	257	51.4 ± 7.7	8	3%
10-day sciatic crush	5	7	240	48.0 ± 10.4	60	23%
Adult spinal nerve freeze	5	7	390	78.0 ± 7.2	89	23%
Adult spinal nerve crush	5	6	264	52.8 ± 21.8	93	35%
10-day spinal nerve crush	5	9	359	71.8 ± 7.9	258	72%

Crushing of Adult Rat Sciatic Nerve

In 5 adult rats the sciatic nerve was crushed in the midthigh. The pooled results are shown in the middle row of scattergrams of fig. 2 and are also summarized in Table 1. The results from individual experiments are given in Table 2. The accuracy of reinnervation is very good as can be seen by comparing the experimental and control scattergrams in fig. 2. Only 3% of cells were located outside the area which enclosed 99% of the cells from the 23 control sides. When data from individual rat experimental left sides were compared with their corresponding control sides only 1 rat showed a significant difference in the mean height of cells in the grey matter, and 1 in the rostrocaudal axis (Table 2).

Crushing of Neonatal Sciatic Nerve

The pooled results from this group of 5 rats are shown in the bottom scattergrams of fig. 2 and are summarized in Table 1. There is a noticeable increase in the degree of abnormality; 23% of all labelled cells lie outside the 99% normal limits of the plantar motor pool. When individual experimental sides were compared with their corresponding control sides, significant differences were detected in every case either in one or more axes (*see* Table 2). Study of the lateral view of the cord in the bottom right scattergram of fig. 2 shows that the most prominent abnormality is the addition of an anteriorly placed group of cells with a mean vertical height of 82%.

Crushing of Adult Lumbar Spinal Nerves

The pooled results from this group of rats are shown in the middle pair of scattergrams of fig. 3 and summarized in Table 1. This procedure results in over a

TABLE 2 COMPARISON OF LEFT (EXPERIMENTAL) AND RIGHT (CONTROL) SIDES FOR INDIVIDUAL EXPERIMENTS

Experiment		*Horizontal axis*	*Vertical axis*	*Rostrocaudal axis*	*Fraction of cases where control and experimental sides differ significantly*
Adult sciatic nerve crush	1	−	−	−	2/15 = 13%
	2	−	+	−	
	3	−	−	−	
	4	−	−	−	
	5	−	−	+	
10-day-old sciatic nerve crush	1	+	−	+	11/15 = 73%
	2	+	+	+	
	3	+	+	+	
	4	−	+	+	
	5	−	+	−	
Adult spinal nerve freeze	1	+	+	+	9/15 = 60%
	*2	−	−	+	
	*3	−	−	+	
	4	+	+	+	
	5	+	−	−	
Adult spinal nerve crush	1	+	+	−	12/15 = 80%
	2	+	+	+	
	3	−	−	+	
	4	+	+	+	
	5	+	+	+	
10-day-old spinal nerve crush	1	+	+	+	15/15 = 100%
	2	+	+	+	
	3	+	+	+	
	4	+	+	+	
	5	+	+	+	

* In these 2 experiments the experimental side was compared with the mean of the control sides of the other 3 experiments in the group. + = the mean position of the cells in the experimental and control sides differ significantly according to Student's t test ($P < 0.05$, two-tailed test).

third of the labelled neurons having abnormal positions within the spinal cord. When comparing individual experimental and control sides it was found that in 3 rats the mean positions of labelled cells were significantly different in all 3 axes (*see* Table 2). Thus crushing of spinal nerves in adult rats leads consistently to large numbers of errors on reinnervation. Inspection of the middle row of scattergrams in fig. 3 shows that a large proportion of the abnormally positioned cells are placed anteriorly to the normal plantar pool. This group of anteriorly misplaced cells has a significantly different population from the abnormal group which labels after crushing the sciatic nerve in 10-day-old rats ($P < 0.005$).

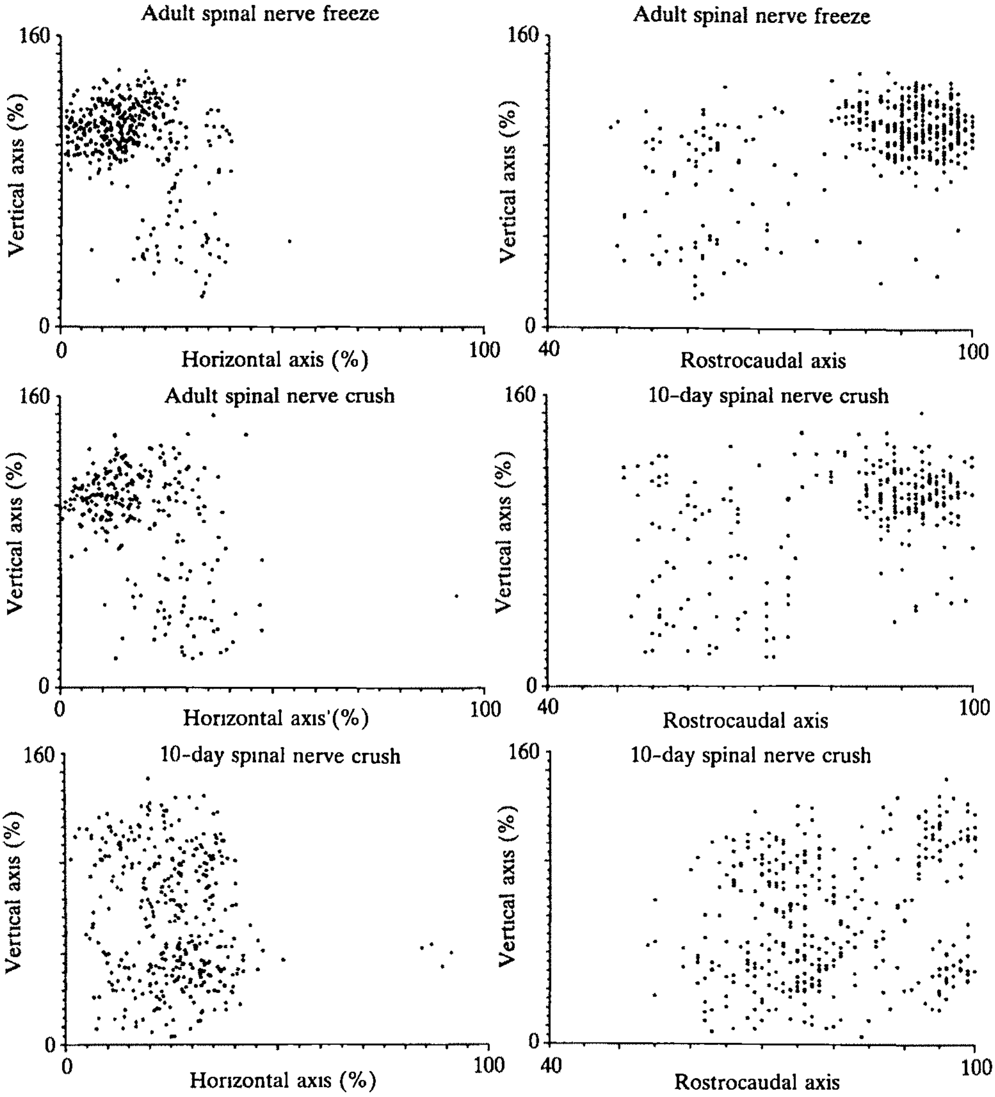

FIG. 3. Scatter diagrams as in fig. 2. *Top panels*, freezing of the lumbar spinal nerves in 5 adult rats; *middle panels*, crush of lumbar spinal nerves in 5 adult rats; *bottom panels*, crush of lumbar spinal nerves in 5 neonatal rats.

Freezing of Adult Lumbar Spinal Nerves

The top row of scattergrams in fig. 3 and Table 1 summarize the data for the 5 rats in this series. The results seem to be similar to but slightly less extreme than those seen after crushing adult rat spinal nerves with forceps. Only 23% of cells were abnormally placed, although the pooled experimental data differed significantly from the pooled data from the control sides in all 3 axes. In all 5 individual animals the experimental side results differed significantly ($P < 0.05$) from the control side in one or more axes (*see* Table 2).

Neonatal Crush of Spinal Nerves

The results are summarized in the bottom scattergrams of fig. 3 and Table 1. Data for individual experiments are given in Table 2. This procedure had a drastic effect, causing a substantial majority (72%) of the neurons sending axons down the plantar nerve to come from abnormal spinal sites in all 5 experiments. As can be seen in the scattergrams it is no longer possible to make out the normal group of plantar neurons, as the labelled population seems to be scattered randomly throughout the ventral horn. This very abnormal anatomy correlated with the abnormal leg movements made in those rats operated on when 10 days old.

Numbers of Labelled Cells

The mean number of cells labelled in each experimental group is given in Table 1. As can be seen, this varied substantially and the size of the SEs shows that within each group there were also large variations from animal to animal. We believe that some of these differences are probably due to experimental difficulties rather than just reflecting a variable degree of reinnervation. In many rats it was very difficult to stop the central plantar nerve stump from bleeding into the HRP-containing suction pipette, and this probably prevented access of label to all the axons. The right (control) side was always labelled after the experimental side and this might account for the fact that in 2 rats no cells labelled, and in the others the mean number of cells labelled was lower than on the experimental side. However, we cannot rule out the possibility that newly regrown axons are better transporters of HRP than normal axons as has been suggested (Kristensson and Sjöstrand, 1972).

DISCUSSION

There can be no doubt from the results presented here that neither crushing nor freezing of peripheral nerves is followed by perfect reinnervation. The amount of misdirection, however, varies considerably depending on the age of the animal and the site of the lesion. We discuss below how these differences might arise.

Differences between Neonatal and Adult Nerves

The larger number of mistakes made by the axons regrowing in neonatal rats suggests that the endoneurial sheaths are more easily penetrable and/or damaged at this age. We could not in fact be sure whether the growth cones were penetrating completely intact sheaths or growing through microscopic defects created by mechanical damage. In the neonate where the collagen scaffold for the endoneurial tubes is probably less well developed this could have occurred more readily. Another factor tending to increase errors in neonates might be the overall smaller size of the nerve at the time of operation, which might make it more susceptible to mechanical damage. We attempted to find out whether direct mechanical trauma inflicted by the forceps to endoneurial sheaths created all the routes through which regrowing axons escaped. This we did by comparing the accuracy of reinnervation following a crush to the spinal nerves of adult rats (which we had by then shown to cause extensive errors) with the accuracy following a cryolesion of the spinal nerves. The percentage of incorrectly projecting axons was only a little less after freezing the spinal nerves (*see* Tables 1, 2). This leads us to believe that regrowing axon sprouts can, in a significant proportion of cases, escape from intact endoneurial tubes, just as they can during nodal sprouting from intact nerves.

Differences between Spinal and Peripheral Nerves

As far as we are aware no difference exists in the connective tissue sheaths in spinal nerves proximal to the plexuses and peripheral nerves distal to the plexuses that could account for the difference in the results of lesions in the two places (*see* Low, 1976). (Major differences in structure do, of course, exist between spinal *nerves* and spinal *roots* but we are not in our experiments concerned with the roots.) In the absence of a structural difference an alternative explanation for the difference between the results of sciatic lesions, which in the adult repair extremely accurately, and spinal nerve lesions must be found. One possibility is the different disposition of axons in the two sites as described in the Introduction. In the spinal nerves where axons destined for a particular muscle do not lie side by side but are intermingled with axons with other peripheral targets (Landmesser, 1984), the exchanging of endoneurial sheaths by regrowing axons will inevitably lead to far more overt errors than can arise in the sciatic where axons are associated largely with others with similar destinations. The possibility cannot, however, be entirely excluded that in the spinal nerves proximal to the sciatic plexus axons have no guidance (hence their intermingling) but in the nerves distal to the plexus some form of guidance may exist even in adults (Politis, 1985) as it does in embryogenesis (Landmesser, 1984).

Relation of Present Results to Those of Others

Work by Lowrie *et al.* (1982) who examined the effect of sciatic crush lesions on 7-day-old rats provided evidence that axons reinnervating the tibialis anterior muscle and the extensor digitorum longus muscle come from entirely normal locations. Our data (fig. 2, bottom row) show that most of the errors made after the sciatic crush in neonates come from motoneurons more rostrally placed in the cord. It is possible that Lowrie *et al.* did not examine parts of the cord anterior to the normal tibialis and extensor digitorum pool and so missed any errors that might have occurred.

Conclusion

Our overall conclusion is that crush lesions and cryolesions are not followed by perfect repair because regrowing axons can cross endoneurial walls even though the longitudinal continuity of these sheaths has not been broken. The effect of such exchanges is considered to be minimal in peripheral as opposed to spinal nerves because of the ordered distribution of axons in distal nerves such as the sciatic. In addition crush lesions to neonatal nerves cause more misrouting of regenerating axons than equivalent lesions to adult nerves.

ACKNOWLEDGEMENTS

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LONG-LATENCY SPINAL REFLEX IN MAN AFTER FLEXOR REFLEX AFFERENT STIMULATION

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SUMMARY

Electromyographic (EMG) flexor muscle responses evoked by electrical stimulation of ipsilateral peripheral nerves were studied in 16 patients with clinically complete spinal cord transection. Stimuli were applied either to a cutaneous nerve (sural) or to a mixed nerve (tibial) and muscle responses were recorded from tibialis anterior, biceps femoris and rectus femoris. EMG recordings after both sural and tibial nerve stimulation showed that distinct early and late ipsilateral flexor muscle responses could be elicited. This distinction was more evident for tibialis anterior. The latency of the early responses averaged approximately 100 ms with sural and 75 ms with tibial nerve stimulation. This corresponds to the latency of the flexion withdrawal reflex previously described in normal man. After sural stimulation, the early reflex appeared in biceps femoris at a threshold intensity not significantly different from that in normal man given the same stimulation parameters. Late responses appeared after a longer latency (130 ms) and at a lower threshold than the early flexor reflex. In all patients a striking feature of the late response was that its latency increased with increasing stimulus intensity, the maximum latency being as long as 450 ms. This increase also occurred with increasing duration of high intensity stimulus trains.

Neither the appearance of a late response nor its latency increase could be explained by a peripheral loop due to a preceding muscle contraction (from either motor axon stimulation or motoneuronal discharge corresponding to the early flexion reflex). It was therefore concluded that both were directly elicited by the afferent volley set up by electrical stimulation. The low threshold of the late reflex corresponded to the excitation of relatively rapidly conducting afferents and its central spinal delay was more than 100 ms. The late reflexes were compared with those described by Andén *et al.* (1964) in the acute spinal cat injected with DOPA and were found to have similar characteristics. The mechanism for the increase in latency of the late response is discussed in relation to the interpretation of Lundberg (1979).

INTRODUCTION

A flexion reflex, similar to the flexion withdrawal reflex described in the spinal cat by Sherrington (1910), has been observed in man. After cutaneous stimulation or electrical stimulation of peripheral nerve, an electromyographic (EMG) response can be recorded in flexor muscles with a latency of less than 110 ms; this has been

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described as a flexion reflex (Pedersen, 1954; Hagbarth, 1960; Kugelberg *et al.*, 1960; Hugon, 1967). It is evoked by nociceptive stimuli. Similar flexor responses can be recorded in patients with complete spinal cord transection after recovery from spinal shock (Pedersen, 1954; Dimitrijević and Nathan, 1968). We will denote this reflex the *early flexion reflex.*

In spinal patients, longer latency responses have also been mentioned although not studied thoroughly (Rushworth, 1966; Dimitrijević and Nathan, 1968; Shahani and Young, 1971). The present investigation was therefore undertaken to analyse the characteristics of this late response. In a group of 16 patients with clinically complete spinal cord transection, the latency of the flexor EMG responses observed after distal electrical limb stimulation was studied with reference both to the early flexor reflex and to the long-latency reflex described in the acute spinal cat injected with DOPA (for review, *see* Lundberg, 1979). It has been shown in the cat that this latter reflex differs from the short-latency flexion reflex and is related to an interneuronal network likely to be responsible for spinal stepping (Jankowska *et al.*, 1967*a*; Lundberg, 1981).

METHODS

The 16 patients included in this study (13 men and 3 women, aged 18 to 45 years) suffered from complete traumatic paraplegia. All were volunteers and fully informed of the experimental aim of the procedure. Although the spinal cord section had never been verified surgically, it was considered complete on the basis of clinical examination: below the level of the lesion (from C6 to T8), all patients were incapable of any voluntary movement and sensory loss was total. In addition there was no recovery during the subsequent clinical follow-up period of at least one year after the experiment.

The time-span between the spinal cord lesion and the experimental session (one month to fourteen years) permitted patients to be examined after the end of spinal shock. Before the experiment the presence of flexion responses in the tibialis anterior (TA) muscle was tested by stimuli such as scratching the sole of the foot or twisting the toes. At the time of the session, the patients were free from bedsores, urinary infection and other medical complications.

During the session, the patients sat in their wheelchairs or lay on a bed. In both situations the knee and ankle remained semiflexed, supported by pillows. Electrical stimuli were applied percutaneously to nerve trunks by means of two electrodes placed, cathode proximally, on the abrased and degreased skin. The purely cutaneous sural nerve was stimulated in the submalleolar region and the mixed tibial nerve at the ankle. The stimulus consisted of a brief pulse (1 ms duration each) trains delivered at more than 5 s intervals. The frequency and duration of each pulse train varied with the nerve stimulated: 300 Hz for 30 ms (sural), 70 Hz for 40 ms (tibial). Occasionally, train durations of up to 500 ms were used.

The EMG was recorded via bipolar surface electrodes placed on the degreased skin above the ipsilateral flexor muscles: tibialis anterior (TA), short head of biceps femoris (BF), rectus femoris (RF), and the medial hamstrings muscles. When stimulating the tibial nerve, EMG recordings were also obtained from the flexor hallucis brevis (FBH). During each experimental session, 100 to 200 stimuli were delivered with an intensity varying randomly between 0 and 50 mA, measured by a current probe (Tektronix 6021). Additionally, in several patients, full-wave rectified averages of five EMG responses were obtained for each stimulus intensity. An analog-digital converter linked to an Apple II microcomputer permitted measurement of current probe output amplitude, latency of EMG responses and the area of the full-wave rectified EMG.

RESULTS

Sural Nerve Stimulation

EMG recordings of lower limb flexor muscles (TA, BF, RF) were made in 13 subjects after ipsilateral sural nerve stimulation of randomly varied intensity (0–50 mA).

Tibialis anterior responses. The EMG response was recorded in TA in all 13 subjects. As illustrated in fig. 1 the records showed two distinct components (1) an early response, with a latency of about 100 ms not regularly observed (it was never observed in subject H.A. (fig. 1A) and only irregularly in subject A.N. (fig. 1B), whatever the stimulus intensity); and (2), a late response (present in both these subjects), the latency of which varied with the stimulus intensity and was always longer than 160 ms (compare traces a and b, c and e, d and f). The occurrence of the late response was independent of whether or not an early

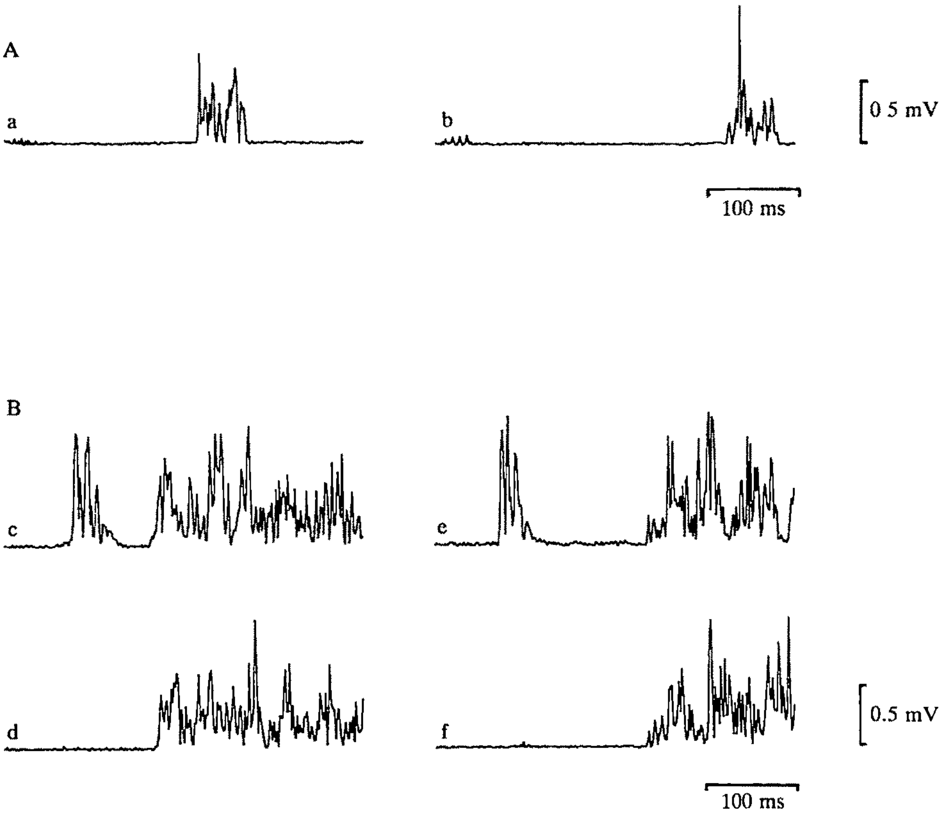

FIG. 1. Tibialis anterior responses after sural nerve stimulation. Examples of rectified EMG traces for different stimulation intensities. A, results obtained in subject H.A. Stimulus intensities a, 15 mA; b, 30 mA. B, results obtained in subject A.N. during the same experimental session. *Upper traces* (c, e) show an early response followed by a late one, *lower traces* (d, f) a late response appearing alone for the same stimulus intensity Stimulus intensities; c, d, 12 mA; e, f, 20 mA.

response occurred, indicating that its mechanism was worth investigating in its own right.

The early responses (latency 103 + 11 ms) were observed in 5 out of the 13 subjects. Even in these 5 subjects it was not constant; it occurred in 5% to 47% of the responses recorded. In 1 patient this early response appeared only at low intensity, but in the others, as in fig. 1B, above a given threshold it appeared whatever the stimulus intensity. The duration of the response was never longer than 50 ms and the latency was not modified with increase in stimulus strength (in fig. 1B, compare c and e).

The late responses appeared in all 13 subjects, although they were occasionally absent in 5 of them. Usually they appeared as a short burst (fig. 1A), eventually followed by several iterative rhythmical responses (*see* fig. 6A).

The striking characteristic of the late response was the increase of its latency with increasing stimulus intensity. This change was studied systematically by plotting the response latency against stimulus intensity. Fig. 2 shows results obtained in 2 subjects. In subject H.A. (fig. 2a), the late response appeared with a latency of 210 ms for stimuli stronger than 7.5 mA. The latency increased for stimuli above 15 mA and then continued to increase linearly up to more than 450 ms obtained at 46 mA. With even stronger stimuli, the late response disappeared altogether. In subject A.N. (fig. 2B), the results were somewhat different. In this patient, the irregular early response latency, which is also plotted (black triangles), averaged 109 ± 16·9 ms and did not change with variations in stimulus intensity. The late response appeared at 2 mA with a highly variable latency which decreased to 170 ms at 3 mA. After this initial decrease, the latency of the late response increased with the stimulus intensity. The curve for the latency increase was linear up to 380 ms, obtained with a 35 mA stimulation, following which the increase in slope was less. The latency of the late response followed the same pattern whether it appeared alone (circles), as was usually the case, or whether it was preceded by an early response (open triangles).

At a given stimulus strength the latency of the late response was the same whether or not the early reflex response had occurred (figs 1B, 2B). It can therefore be assumed that the spinal effects of the early homonymous alpha motoneuron discharge (after-hyperpolarization, Renshaw inhibition and afferents stimulated by muscular contraction) do not play any significant role in the occurrence and increase of TA late response latency.

The threshold intensity for the late response ranged from 1 to 7.5 mA (mean 3.3 ± 2 mA) in all subjects. At low stimulus intensities (less than twice threshold for the response), the latency of the late response decreased in 4 subjects when the strength of stimulation was increased, as illustrated in fig. 2B. In the 9 others (*see* fig. 2A), the minimum late response latency was observed at threshold. This difference was not linked to the presence of an early response, which was present in 2 patients of the former group and 2 patients of the latter. A decreasing response latency must be considered as characteristic of the late response per se in some subjects and independent of the occurrence of the early response. This is clear from cases where both responses were observed (figs 1B, 2B): a late response with decreasing latency could be preceded by an earlier one of short duration which did not usually overlap it.

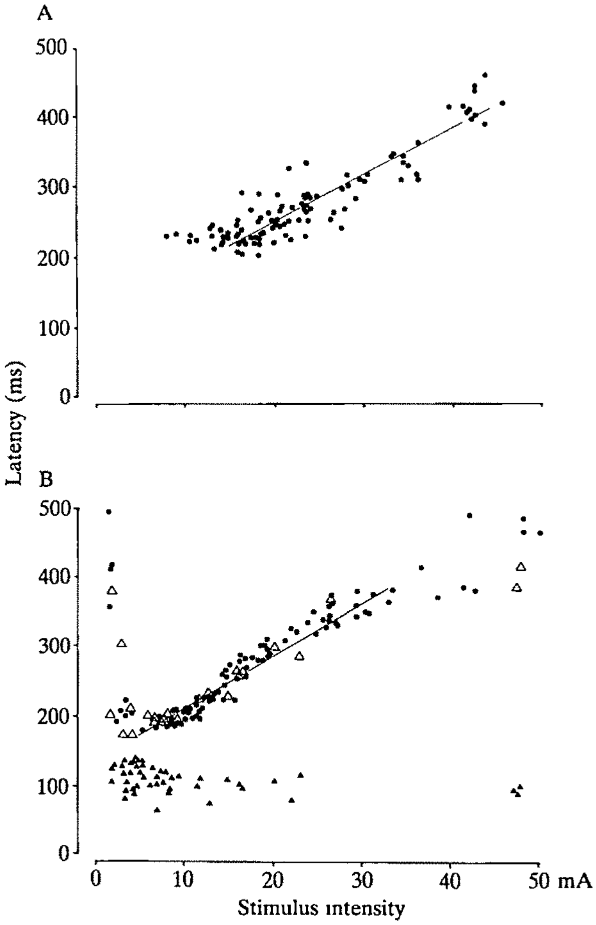

FIG. 2. Latency of the responses in tibialis anterior after sural nerve stimulation, plotted as a function of stimulus intensity. Calculated regression lines. A, subject H.A. The late response appeared to be isolated ($r = 0.92$, $P < 0.001$). B, subject A.N. A late response is irregularly preceded by an early one. Filled triangles indicate early reflex, filled circles an isolated late reflex and open triangles a late reflex preceded by an early one. The regression line ($r = 0.96$, $P < 0.001$) is for the linear portion of the response for the isolated late reflex.

With increased stimulus intensity, an increase in the latency of the late response was observed in all subjects. Regression lines were calculated for the range of linear increase of latency with stimulus strength (corresponding to the segment line on figs 2A, B). The slope of these regression lines was significantly different from zero in all subjects ($P < 0.001$ in 11 subjects, < 0.02 in 2). The minimum intensity above which increase of stimulus strength induced a latency increase ranged from 3 to 18 mA (mean 8.65±4.6) and the corresponding minimum latency of the late response ranged from 130 to 220 ms (mean 166.2±25.3). The latency of the late response increased up to a maximum of 401.5±75.9 ms, obtained for intensities ranging from 15 mA to 50 mA (maximum delivered), depending on the subject (mean 31.2 ± 10.8). The difference between minimum and maximum late response latency was highly significant ($P < 0.001$, Student's paired t test).

In 1 subject, a linear latency increase was observed up to a maximum of 50 mA. In 2 subjects, the maximum latency obtained remained constant or increased only slightly on further intensity increases, the curve exhibiting a plateau. In 8 subjects, the late response disappeared at high stimulation intensities (fig. 2A).

The variation of EMG corresponding to the late response is illustrated on averaged EMG traces in fig. 3A, B. As the latency increased, EMG activity decreased in amplitude and duration and disappeared (fig. 3A).

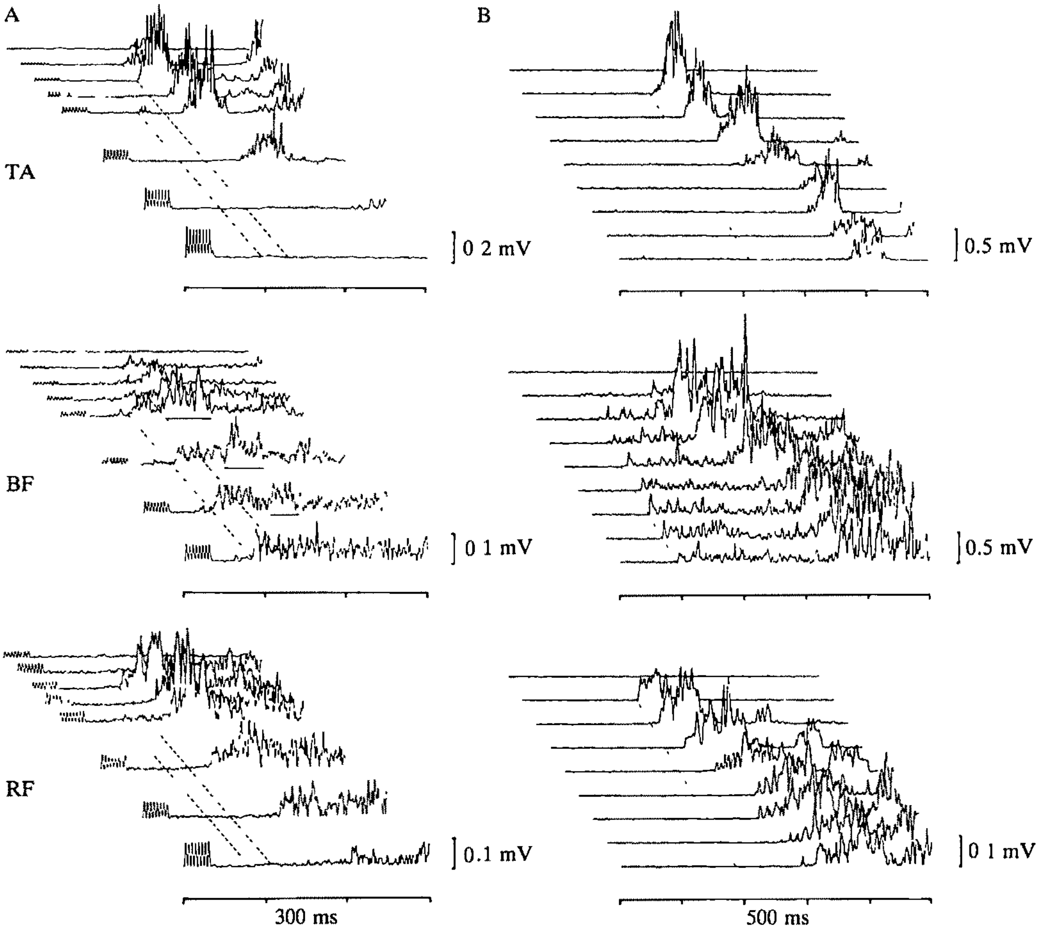

FIG. 3. Examples of simultaneous responses in tibialis anterior, biceps femoris and rectus femoris after sural nerve stimulation in 2 subjects. Each trace represents the average of 3 individual rectified EMG recordings. For each muscle, the *upper trace* was obtained after the lowest stimulation intensity. In A (subject N.O.) the stimulation intensities are respectively 1, 3, 6, 9, 12, 20, 30 and 40 mA. In B (subject F.A.) the stimulation intensity increase from 5 to 45 mA by 5 mA steps. In A, the possible late increase of EMG activity in biceps femoris is underlined.

Biceps femoris responses. Representative EMG responses from BF are illustrated in fig. 3A, B. In both subjects, the response appearing at low stimulus strengths had a long latency. In subject F.A., it was evoked at 10 mA with a 210 ms latency, in subject N.O., at 3 mA with a 130 ms latency. In 10 subjects, the late response clearly appeared with a latency higher than 130 ms at a lower threhold (5.58 ± 2.7 mA) than the threshold for the early response. Stronger stimuli (15 mA in subject F.A., 6 mA in subject N.O.) produced an early response with a latency of 100 and 90 ms, respectively. With increasing stimulus strength, the early response became larger and was followed by a tonic EMG discharge of long duration which perhaps can be described as an afterdischarge. This tonic activity made a precise study of the latency of the second response difficult. Nevertheless, the averaged rectified EMG traces showed a late increase of EMG activity in BF as shown in subject F.A. (fig. 3B) and in 2 other subjects, but was much more difficult to see in the others (underlined in fig. 3A). The latency of this increase, when possibly detected, was similar to the latency of the late EMG response observed in T.A. and increased along with increasing sural nerve stimulus intensity. Note that in subject F.A. (fig. 3B) the duration of the late EMG increase was also prolonged.

An early BF response appeared in all subjects. Stimulus intensities of more than 11.4 ± 6.8 mA always induced an EMG response beginning 98 ± 6.8 ms after sural nerve stimulation. The size of this response, measured by the area of the rectified EMG 90 to 160 ms after the onset of the stimulus, progressively increased with stimulus intensity before reaching a maximum (fig. 4B). In addition, stimulus intensities higher than 21.3 ± 9.4 mA induced a phasic response with a latency of 74 ± 8 ms in 7 subjects.

Rectus femoris responses. EMG responses in RF are illustrated in fig. 3A, B. In the 2 subjects illustrated, a late response was observed with a latency which increased with increasing stimulus intensity. In both cases, the duration of the response was longer and the latency shorter than for TA. The latency difference was too large (about 80 ms for the highest stimulus intensity) to be explained by the more proximal location of RF.

Five subjects were studied. In 2, early responses were obtained with a latency (90 and 105 ms) which was not modified by increasing stimulus intensity. Late responses appeared in all subjects at a strength of 4.2 ± 2.3 mA. A latency increase was observed in 3 subjects. In 1 of them, it was preceded by a decrease in the latency of the late response slightly above threshold for the response; in another the latency of the late response also decreased for intensities near threshold intensities but then remained constant (140 ms). In the last subject, a significant decrease in the latency of the late response (from 280 to 190 ms) was observed for intensities between 4 to 40 mA.

In 4 subjects, medial hamstrings muscle activity was recorded. Visual examination of EMG traces showed that the latency of the late response varied in the same way as for TA. An irregular and higher threshold early response was recorded, followed by tonic activity in 1 patient.

In brief, stimulation of the sural nerve evoked two distinct EMG responses, an early and late, in ipsilateral flexor muscles. The early response was not constant, except in BF, and its threshold was usually higher than that for the late response in the same muscle. Late responses appeared in all flexor muscles. An increased latency of the late response with increased stimulus intensity was found in all flexor muscles, although irregularly in RF.

Relations between the early and late responses in different muscles. It could be imagined that all the EMG responses could be attributed to the classical flexor reflex, the gap between early and late responses being caused by an inhibition following the early response. As has been shown previously, the early response in TA had no effect on the homonymous late response. We shall now examine the effect induced by the early responses of other muscles on the late response in TA.

Ipsilateral extensor muscles (soleus and vastus intermedius) cannot be involved because no EMG activity was obtained in these muscles during 500 ms after the onset of sural nerve stimulation.

The occurrence of a late response in TA was not due to early responses in heteronymous flexor muscles since they were not consistently evoked, except in BF, and usually had a higher threshold. Nevertheless, an early response in other muscles might have accounted for the increase in latency of the late response in TA. For example, an early response in BF was constant and appeared at a stimulation intensity of 11.4±6.8 mA. This intensity was not significantly different from that of 8.65±4.6 mA which induced the increase in latency of the late response in TA. The relation between the early reflex in BF and the latency of the late response in TA was therefore studied systematically.

The possibility that the late response in TA could appear at the end of an inhibitory process linked to motor activity in BF seemed unlikely. Indeed, inspection of EMG traces showed that the duration of tonic activity in BF increased with stimulation intensity and exceeded the latency of the late response in TA in all subjects (a late response in BF notwithstanding).

The relation between the latency of the late response in TA and the corresponding early discharge in BF was studied systematically. Both the area of the rectified EMG in BF (90 to 160 ms after the onset of stimulation) and the latency of the late response in TA were plotted against the intensity of stimulation. As illustrated in fig. 4, the latency of the late response in TA still increased for intensities beyond that which induced the maximum early response in BF.

Correlation coefficients were calculated in 9 subjects for sural nerve stimulus intensity, the latency of the late response in TA, and the area of the rectified EMG response in BF (corresponding either to a distinguishable EMG early response or to the beginning of tonic EMG activity).

Calculations were made on data corresponding to those stimulations inducing a linear increase of the latency of the late response in TA (e.g., figs 2, 4). Correlation coefficients between the area of the rectified EMG response in BF and stimulus intensity were significant (e.g., $r = 0.805$, $P < 0.001$ for the subject in fig. 4).

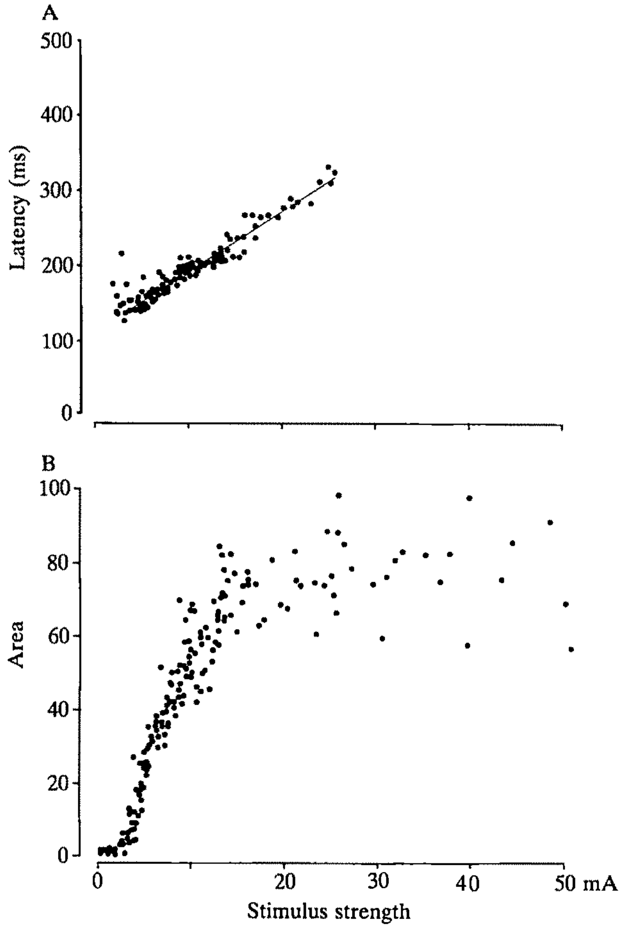

FIG. 4. Comparison of the latency of the late response in tibialis anterior (TA) and the area of the early response in biceps femoris (BF) simultaneously recorded in one subject (N O.). A, latency of TA response as a function of sural nerve stimulation intensity. Calculated regression line ($r = 0.97$, $P < 0.001$). B, area of rectified EMG (in arbitrary units) corresponding to the early response in BF (between 90 and 160 ms after the onset of sural nerve stimulation) as a function of stimulus intensity ($r = 0.805$, $P < 0.001$). For a multiple correlation analysis between the latency of the late response in TA and the area of the early response in BF, for constant stimulation intensity, $r = 0.125$ (n.s.).

Multiple correlation coefficients calculated for constant intensity showed that the correlation observed between the early EMG response in BF and the latency of the late response in TA depended only on the intensity of stimulation ($r = 0.125$ for subject fig. 4, n.s.). Thus neither the recruitment of the late response in TA nor its latency increase were linked to the early EMG response in BE. The appearance of a late response in TA and its latency is thus not significantly dependent on the early response, evoked either in TA or in other muscles.

Tibial Nerve Stimulation

Stimulating a mixed nerve allows comparison of afferent effects in relation to alpha motor axon threshold, measured by the direct motor response. The response in TA to tibial nerve stimulation was studied in 8 subjects.

The left side of fig. 5 shows the motor response in FHB (M) appearing after the first shock and the right side the simultaneous recording of the EMG in TA. A late response appeared, with a latency of 175 ms for a stimulus intensity below motor threshold (MT). For stimulus intensities between 1 × MT and the lowest intensity necessary to obtain a maximum M response (MMT) (when all alpha motor axons were recruited), the latency of the late response in TA decreased to 150 ms. The increase of the latency of the late response appeared for stimulus intensities higher than 1 × MMT, and for the maximum intensity used here (3.5 × MMT), it attained 390 ms.

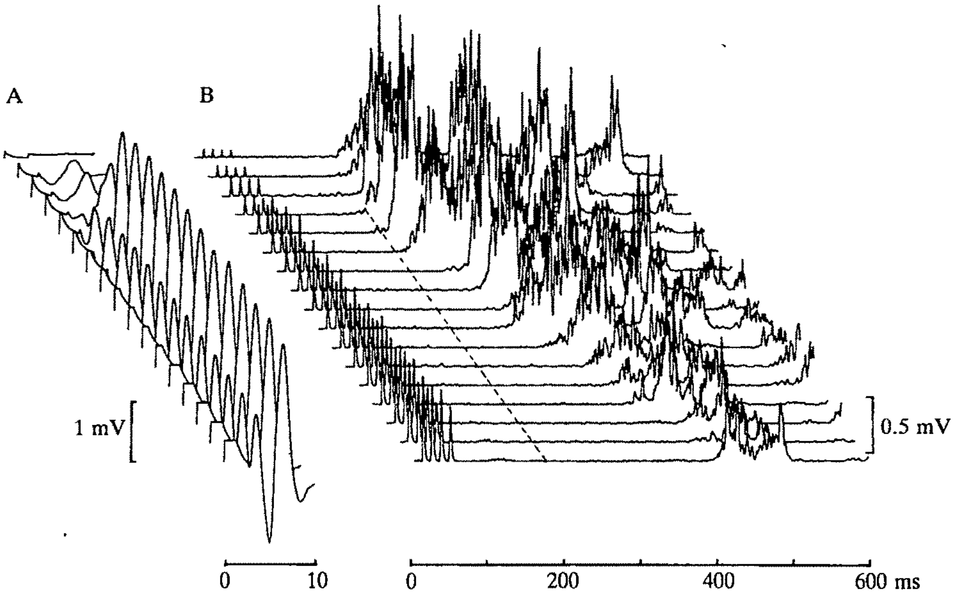

FIG. 5. Comparison of the late response in tibialis anterior (TA) and the simultaneous direct motor response in flexor hallucis brevis (FHB) after tibial nerve stimulation in one subject (A.N.T.) Stimulation intensity increases from 4 (*upper traces*) to 68 mA (*lower traces*) in 4 mA steps. A, FHB M response. Each trace represents an EMG recording after the first shock of the stimulus train. B, simultaneous TA response. Each trace represents the average of three individual rectified EMG recordings.

The threshold of the late response in TA averaged 0.75 + 0.58 × MT in all subjects. This implies that a late response can be obtained from afferent fibres with faster conduction velocity than alpha axons. In all subjects, a gradual increase of the stimulus intensity above 3.07 + 1.1 × MT or 1.4 + 0.42 × MMT induced a successive increase in the latency of the late response in TA. Thus this increase is not linked to direct motor axon stimulation or the muscular contraction.

An early TA response was observed in 3 subjects with a latency (70–75 ms) which was unaltered by increases in stimulus intensity. It appeared regularly, provided that stimulus intensity was sufficiently high. In 2 subjects the threshold of the early response was higher than that for the late response. Additionally, EMG responses in BF and RF after tibial nerve stimulation were studied in 3 subjects. The results were equivalent to those obtained with sural nerve stimulation.

Effects of Increasing Stimulus Train Duration (Tibial Nerve)

Increasing stimulus intensity prolongs the duration of the afferent discharge at the level of the spinal cord through afferent asynchrony. When slowly conducting afferents are recruited this effect is particularly marked in man where the distance between ankle and spinal cord is more than 1 m. The effect on TA responses of increasing the duration of stimulus trains delivered to the tibial nerve from 50 to 500 ms was investigated in 7 subjects. As before, trains of shocks 1 ms in duration with the same internal frequency (70 Hz) were used.

Fig. 6 shows the results in 2 subjects. The right side shows the TA EMG obtained in one subject (A.N.T., fig. 6B) when the train duration was increased at three stimulus intensities. After stimulation at 1 × MT, the latency of the late response was slightly decreased when the train duration was increased from 45 to 150 ms. When the train intensity was raised to 1 × MMT, a late response appeared with a greater amplitude and a shorter latency regardless of the duration of the train. When the stimulus intensity was 2 × MMT, the onset of the late response was well

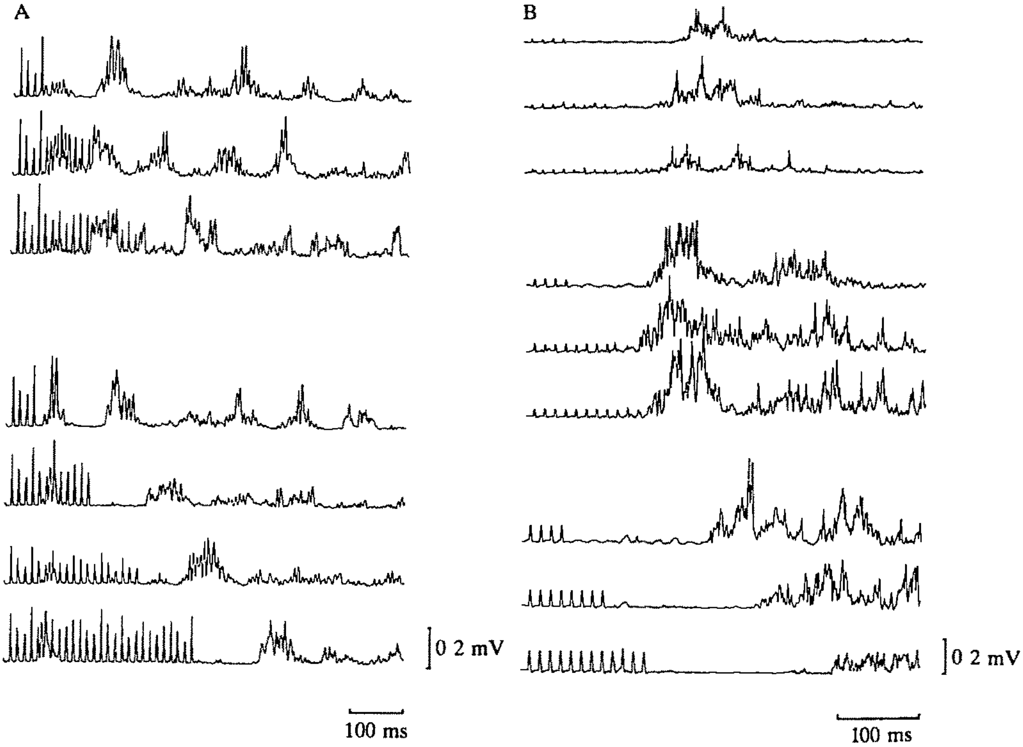

FIG. 6 Effect of increasing train duration on the TA response after tibial nerve stimulation Recordings from 2 subjects. Eact trace represents the average of three individual rectified EMG recordings. The stimulus artefact shows the train duration. A, subject H.E. Effect of increasing train duration (60, 160, 260 and 360 ms) for intensities of 2 5 (*upper 3 traces*) and 3.5 × MMT (*lower 4 traces*). B, subject A.N.T. Effect of increasing train duration (45, 95 and 150 ms) for intensities of 1 × MT (*upper 3 traces*), 1 × MMT (*middle traces*) and 2 × MMT (*lower 3 traces*).

defined and always appeared about 200 ms after the end of the train, regardless of its duration. In another subject (H.E., fig. 6A) both the early and the late response were recorded. Increasing the 2.5 × MMT train duration from 60 to 160 ms did not modify the early response but slightly decreased the latency of the late response. For 3.5 × MMT stimulation, the latency of the late response increased with increasing train duration. These strong stimuli of long duration did not prolong the duration of the early response.

Similar results were obtained in 6 subjects. At high stimulus strength (1.5 to 3.5 × MMT) an increase in the latency of the late response in TA was clearly observed in all subjects, regardless of train duration. The required stimulus intensity was higher in all subjects than the minimum intensity which induced a latency increase when train duration was kept short (40 ms).

Increasing the duration of low range stimulus trains (lower than 1 × MMT) induced a decrease in the latency of the late response and increased the duration and the amplitude of the late response. The onset of the late response was sometimes intermingled with the end of the early response, when this one was present. For stimuli of medium intensity, stronger than 1 × MMT, the effect of increasing train duration varied with the duration used. For example, the latency of the late response in TA was clearly increased when increasing train duration from 50 to 100 ms, but did not increase further for longer train durations.

Afferents Involved in Latency Increases

When train duration was within 30 to 40 ms the increase in latency appeared at a definite intensity corresponding to 1 × MMT after tibial nerve stimulation. This suggests that the increase of the latency is linked to the recruitment of certain afferent fibres.

It can be assumed that stimulation was efficient in increasing the latency of the late response in TA only as soon as it excited afferent fibres thinner than the slowest alpha motor axons. This suggests that the increase in the latency of the late response is linked to the stimulation of afferent fibres for which conduction velocity may be calculated by reference to that of alpha motor axons. Borg *et al.* (1968) showed that velocity for alpha motor axons to extensor digitorum brevis in man ranged from 30 to 54 $m \cdot s^{-1}$. If it is assumed that the velocity for alpha motor axons to FHB is in the same range, latency increases are most likely to be linked to the recruitment of afferent fibres with a velocity of less than 30 $m \cdot s^{-1}$, that is, cutaneous Aδ fibres for which peak velocity is 20 $m \cdot s^{-1}$ (Kimura, 1983) and muscular group II and III afferent fibres. The peripheral conduction time of unmyelinated fibres (conduction velocity 0.5–2 $m \cdot s^{-1}$ over a distance of 1.2 m) excludes their participation in responses occurring 500 to 1000 ms after the onset of stimulation. Accordingly the late flexor reflex appearing in patients with spinal cord lesion after mechanical activation of foot skin C fibres (Kugelberg, 1948) appeared at a latency of 1500 to 2300 ms.

An alternative hypothesis would be that the polysynaptic pathways involved in increasing the latency of the late response need repetitive or more intense afferent activity whatever the velocity range of the afferent fibres involved. If this were the case, increasing train duration would regularly contribute to increasing the latency of the late response. However, the results obtained after a long duration stimulus train of low intensity show that temporal summation mechanisms from large afferent fibres are not efficient enough to increase the latency of the late response. It can therefore be concluded that latency increase is brought about or triggered by afferent fibres thinner than the slowest alpha motor axons, and certainly thinner than those excited at the threshold for the late response.

DISCUSSION

The fact that there are two distinct flexor EMG responses to distal electrical nerve stimulation in patients with clinically complete spinal cord transection raises the question of the respective nature of the early and of the late response.

The Early Response

Early responses have been previously described in patients suffering from spinal lesions by Pedersen (1954), Dimitrijević and Nathan (1968) and Shahani and Young (1971) using electrical stimulation. Comparison can be made with the well known early flexion reflexes described in normal man with respect to latency, muscular activation pattern and electrical threshold.

In normal subjects, the latency of the flexor reflex obtained by electrical stimulation of the distal part of the lower limb is usually shorter than 110 ms. Sural nerve stimulation within the nociceptive range induces a response with a latency of 85 to 120 ms in BF and in other flexor muscles as shown by Hugon (1967) and interpreted as the nociceptive flexion reflex. Stimulation of the tibial nerve produces a response in flexor muscles with a latency of 50 to 60 ms in TA in normal subjects (Pedersen, 1954). Other authors (Kugelberg *et al.*, 1960; Shahani and Young, 1971), by stimulation of the plantar skin (which is innervated by the tibial nerve) have obtained a response with a latency of 50 to 60 ms in TA. In other studies (the flexion reflex being superimposed on a slight voluntary contraction), Hagbarth (1960) and Meinck *et al.* (1981), stimulated the tibial nerve or the skin at a nociceptive strength and observed an increase of the EMG activity in TA which appeared respectively at about 70 and 40 to 60 ms after the onset of the stimulation.

Our results were comparable to those of these authors, since after sural nerve stimulation an early reflex with a latency of approximately 100 ms was regularly observed in BF and irregularly in TA and RF. In the same way after tibial nerve stimulation a reflex with a latency of 75 ms was observed in TA.

The intensity threshold for the early flexion reflex evoked by sural nerve stimulation was measured by Willer (1977) in a group of 15 normal subjects. The threshold for pain sensation was found to be the same as the reflex threshold for the 100 ms latency response in BF (10±1 mA). A mean value (11.4±6.8 mA) for the same 100 ms latency response in BF that was not significantly different was observed here.

The Late Response

It has been shown that the minimum latency of the late response ranges from 120 to 240 ms and that the late response is also characterized by its increase in latency with increasing stimulus intensity. In normal subjects, late responses with a threshold lower than that for the early reflex have not been described. For stimulation intensities in the painful range, lower limb flexor responses with a latency longer than 120 ms have been observed after distal electrical stimulation, but they cannot be distinguished from voluntary responses (Hagbarth and Finer, 1963). In the present study, performed in patients with a complete spinal cord section, the responses can indeed be attributed to spinal reflexes. In such patients, several authors have previously noted that flexor EMG responses could be recorded with a long latency (Rushworth, 1966; Dimitrijević and Nathan, 1968; Shahani and Young, 1971).

The problem arises as to what extent the recruitment of the late response and the increase in latency are due to the effect of the afferent volley set up by electrical stimulation. An alternative hypothesis would be that both are the consequence of a preceding motoneuron discharge and muscular contraction which excites afferent fibres innervating muscle receptors. These events could induce a long-latency EMG response by facilitatory processes or inhibitory ones concealing a part of a long-lasting motoneuronal discharge. Our finding that neither late reflex recruitment in TA nor its latency increase are due to a preceding homonymous or heteronymous alpha motoneuron discharge nor to direct stimulation of plantar alpha motor axons contradicts this hypothesis. Hunt (1951) has shown that stimulation of flexor reflex afferents can induce gamma motoneuron discharge from flexor muscles even without a concomitant alpha motoneuron discharge. However, the latency of such delayed alpha motoneuron activation brought about by the gamma loop would be expected to remain constant. The gamma route is therefore not a likely explanation of the increase of the latency of the late response. Thus the recruitment of a late response and the increase in latency are directly elicited by the afferent volley set up by electrical nerve stimulation.

The late response is different from a long-lasting short-latency reflex afterdischarge (Creed *et al.*, 1932) since afterdischarges are always preceded by pronounced short-latency effects (Jankowska *et al.*, 1967*a*). Here the late response usually appeared alone or independently (fig. 2B) of the early reflex. Moreover, a prolonged strong intensity train (fig. 6A) did not evoke an afterdischarge of long duration but instead a prolonged EMG silent period which preceded the late response.

In the following, this long-latency spinal reflex will be referred to as the *late reflex*.

Central spinal latency of the late reflex. This can be calculated by subtracting the peripheral conduction time from its latency. In the tallest subject studied (1.82 m) the afferent pathway from the ankle to the S1 spinal cord segment was of 1.25 m and the efferent one from L4 to TA, 0.88 m. Thus for TA alpha motor axons with conduction velocities ranging from 30 to 50 $\mathrm{m \cdot s^{-1}}$, the corresponding efferent conduction times would be of 17.5 to 29 ms. After tibial nerve stimulation, the late reflex threshold was less ($0.75 \pm 0.58 \times \mathrm{MT}$) than the threshold for the motor response. It can therefore be assumed that the late reflex is evoked by faster afferents than alpha motor axons. Maximum afferent time may thus be estimated to be less than 26 ms. After sural nerve stimulation, the late reflex appears for stimulation intensities as low as 3.3 ± 2 mA which corresponds (Willer *et al.*, 1978) to the recruitment of low threshold cutaneous afferents belonging to group $\mathrm{A}\alpha\beta$ (conduction velocity 42 $\mathrm{m \cdot s^{-1}}$, Kimura, 1983). The major part of the minimum latency of the late reflex (120–240 ms) is thus caused by a long central spinal delay as the peripheral delay is less than 58 ms.

This long spinal delay of the late reflex suggests a comparison with the long-latency flexor reflex described by Andén *et al.* (1966*a*) in acute spinal cats injected with DOPA (for review, *see* Lundberg, 1979). In the acute spinal cat, DOPA induces the depression of the usual short-latency flexor reflex and the appearance in flexor muscles of a long latency and long duration reflex evoked by stimulation of the same flexor reflex afferents (Andén *et al.*, 1966*a*). Late response central delay calculated here in man was in the same range as that obtained in the cat (100–200 ms, Baldissera *et al.*, 1981). DOPA also induces a depression of the short-latency dorsal root potential (DRP) evoked by flexor reflex afferents in their own terminals and the appearance of a long latency DRP evoked by these afferents in IA terminals (Andén *et al.*, 1966*c*; Jankowska *et al.*, 1966). These findings strongly suggested the existence of separate pathways for the early and the late reflexes and interneuronal recordings proved this to be the case (Jankowska *et al.*, 1967*b*). It was shown that the pathway responsible for the early reflex exerted a tonic inhibition on the pathway responsible for the late reflex. The mechanism of the DOPA effect was shown to be an inhibition of early flexor reflex afferent pathways and thus a release of late reflex pathways by liberating noradrenaline from presynaptic descending terminals (Andén *et al.*, 1964, 1966*b*). The DOPA late reflex has mainly been studied in the acute spinal cat, but has also been observed in the chronic spinal cat (Andén *et al.*, 1966*b*). In the acute spinal cat, either short latency reflexes (before DOPA) or late reflexes (after DOPA) are usually recorded. Nevertheless, a late reflex can also occasionally be observed in the cat without any drug injection when the early flexion reflex is weak (Andén *et al.*, 1966*c*). This establishes (Jankowska *et al.*, 1967*a*) that the early reflex pathway tonically inhibits the late flexion reflex pathway. In chronic spinal man, it is possible that the pathway for the early flexion reflex is less excitable (or its inhibitory influence on the late reflex less important) than is usual in the spinal cat. Therefore in man, the late reflex pathway might be released without drug administration.

Afferents involved in late reflex recruitment. The late reflex in man can be evoked by cutaneous and/or muscle low-threshold afferents presumably larger than the fastest alpha motor axons. The facilitatory effect of afferents of slightly higher threshold is demonstrated by the fact that a moderate increase of stimulation intensity could induce, after stimulation of the tibial or sural nerves, a decrease in the late reflex latency and a corresponding increase in duration and amplitude. As shown in fig. 6, the latency of the late reflex in TA decreased for stimulation intensities recruiting alpha motor axons. This shows that afferents of the same velocity range as alpha motor axons, corresponding to cutaneous or muscular group II afferents, participate in the recruitment of the late reflex.

These results are consistent with data obtained in the acute spinal cat with DOPA. Although the muscle nerves usually had to be stimulated at a strength of 20 to 30 times nerve threshold, a late DRP could be evoked by cutaneous afferents at about twice the nerve threshold, by muscular group II and occasionally by very low threshold group II afferents (Andén *et al.*, 1966*c*). The late reflexes on flexor alpha motoneurons appeared when muscle group III and, occasionally, group II afferents were stimulated; cutaneous (sural) nerve stimulation was also effective at 5 times nerve threshold (Jankowska *et al.*, 1967*a*).

The most striking property of the late reflex in man is the latency increase with increased stimulus intensity or duration which can be compared with the results obtained in cats. A basic similarity between the late reflex in man and that in the spinal cat injected with DOPA is that their latency increases with stimulus duration, since it has been shown that in the cat onset of the late reflex could be delayed after the end of the train regardless of its duration (Jankowska *et al.*, 1967*a*). The increase of the latency of the late reflex with increased stimulus intensity has not been described in the cat. Nevertheless, an increase in the latency of the late reflex with stimulus intensity has been shown when studying the late DRP appearing in Ia terminals after stimulation of flexor reflex afferents (Andén *et al.*, 1966*c*). A late DRP, evoked from low threshold group II afferents, could be delayed and almost abolished when group III afferents were also stimulated. At the same time, increasing the length of the train delayed the onset of the late DRP and decreased the amplitude of the wave. It has been proposed (Lundberg, 1979) that the increase in latency is due to opposite actions produced by the same flexor reflex afferents. Activation of such afferents could induce, on the one hand, late responses (flexor motoneuron activation and DRP) by the long-latency pathway and, on the other, activation of the short-latency pathway, the long-latency pathway being inhibited by the activation of the short-latency pathway at an interneuronal level (Jankowska *et al.*, 1967*a*, *b*). As seen here, the late reflex was elicited by low threshold afferents. Its increase in latency, with increased stimulus intensity or duration was clearly apparent when the stimulation corresponded to the recruitment of afferents slower than 30 $m \cdot s^{-1}$.

The finding that the latency increase is brought about by slower afferents than those inducing the late reflex implies that the intraspinal delay of the pathway which mediates or triggers the inhibition of the reflex is shorter than that of the reflex pathway itself. In man, due to the length of the afferent pathway, the afferent volleys conducted by low and high threshold afferents are largely desynchronized at spinal level. Thus a presynaptic block of low threshold afferent terminals seems unlikely since, at least for short duration trains, a volley in high threshold afferents reaches the spinal cord after the end of the low threshold afferent volley. The results obtained in man do not allow a more detailed discussion of the inhibitory mechanism. A long-lasting inhibition of the flexor motoneurons cannot be excluded but it has never been described in animal experiments. An alternative hypothesis would be an inhibition of the interneuronal pathway mediating the late reflex. This mechanism has been proposed to explain the increase in latency in the cat (Andén *et al.*, 1966*c*) and the tentative wiring scheme proposed by Lundberg (1979) could very well explain the results obtained in man.

In the spinal cat injected with DOPA, late contralateral extensor activity parallels the late ipsilateral flexor activity (Jankowska *et al.*, 1967*a*). Ipsilateral and contralateral stimulation of flexor reflex afferents show strong mutual inhibitory influences on flexor and extensor late responses, and DOPA, when given after a previous injection of nialamide (a monoamine oxidase inhibitor), has been shown to induce alternating stepping-like movements (Jankowska *et al.*, 1967*a*, *b*). This has been taken to suggest an internuncial 'half centre' organization that could subserve locomotor activity (*see* Lundberg, 1981). Accordingly, a late reflex seems always to be present in animal preparations exhibiting locomotor activity (Viala *et al.*, 1974). The present study suggests that some elements of the spinal circuitry on which the generation of stepping rhythms relies in lower vertebrates exist in man.

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NEUROENDOCRINE CONTROL OF VASOPRESSIN SECRETION AND ITS EFFECT ON BLOOD PRESSURE IN SUBJECTS WITH SPINAL CORD TRANSECTION

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SUMMARY

The osmotic and cardiovascular control of arginine vasopressin (AVP) secretion, and the effect of this hormone on cardiovascular regulation were assessed both in normal controls and in subjects with tetraplegia. Infusion of hypertonic saline caused a marked rise in blood pressure in the tetraplegics but not in the normal controls. Head-up tilt resulted in a greater AVP response in the tetraplegics than in the controls because of the additional hypotensive response in the tetraplegics. Infusion of AVP itself at physiological concentrations had little effect on blood pressure in the normal subjects but resulted in a marked rise in blood pressure in the tetraplegics. Tetraplegics therefore show appropriate release of AVP to both osmotic and cardiovascular stimuli but increased sensitivity to the pressor effects of this hormone.

INTRODUCTION

The secretion of arginine vasopressin (AVP) by the posterior pituitary gland is predominantly controlled by two physiological mechanisms: (1) changes in plasma osmolality which are sensed by osmoreceptors in the hypothalamus; (2) changes in blood volume and blood pressure relayed from cardiovascular receptors in the carotid sinus and thorax via the glossopharyngeal and vagal cranial nerves to the nucleus tractus solitarius and thence the paraventricular and supraoptic nuclei of the hypothalamus via predominantly catecholaminergic pathways.

It has been shown previously that subjects with progressive autonomic failure (PAF) have a normal release of AVP to hypertonic saline infusion (Williams *et al.*, 1985*b*), a defective cardiovascular regulation of AVP secretion (Puritz *et al.*, 1983) and an increased pressor response to infusion of this hormone (Williams *et al.*, 1986*a*). Neuropathological examination of these patients shows degeneration

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in catecholamine-containing cerebral nuclei such as the caudate, putamen, locus coeruleus, tractus solitarius and dorsal vagal complex as well as cell loss in the intermediolateral columns and sympathetic ganglia (Spokes *et al.*, 1979; Oppenheimer, 1983). It is therefore difficult to define the cause of their defective release of AVP and increased sensitivity to exogenous AVP. Tetraplegic subjects, however, have in addition to a spinal cord lesion an interruption of their sympathetic outflow but, in contrast to PAF subjects, they have normally functioning glossopharyngeal and vagal cranial nerves and normal central catecholaminergic pathways. We have therefore performed this study in subjects with tetraplegia to assess their control of AVP secretion and to define further the role of the sympathetic nervous system in the haemodynamic responses to AVP in man.

SUBJECTS AND METHODS

Eight male subjects, with a median age of 31 yrs (range 23 to 53 yrs) were studied. All had a complete traumatic cervical (C5–C6) spinal cord transection as evidenced by no detectable somatic motor or sensory function below the level of the lesion on physical examination. Four had lesions of less than 1 yr duration (range 4–8 months) and 4 had lesions of more than 8 yrs' duration (range 8–18 yrs). They were all free of other significant medical problems and were not on any medication that might have affected their blood pressure. Subjects gave their informed consents and the study was approved by the ethics committee at Stoke Mandeville Hospital.

The control group consisted of 7 healthy subjects with a median age of 35 yrs (range 26–57 yrs). Their responses to hypertonic saline (Williams *et al.*, 1985*b*) and AVP infusion (Williams *et al.*, 1986*a*) had already been evaluated. Three separate studies were undertaken.

Hypertonic Saline Infusion

When the subjects had rested supine for 30 min a catheter was inserted into a forearm vein and an intravenous infusion of 0.85 M saline (0.05 ml/kg/min) was commenced and continued for 2 h. Heart rate and blood pressure were recorded at 15-min intervals using an automatic monitor (Sentron, Bard Biomedical). Blood was taken at 30-min intervals from a venous catheter in the opposite arm and the separated plasma subsequently used to measure sodium, osmolality and AVP.

Head-up Tilt

Three days before this study the tetraplegics were tested on a tilt table to determine what angle of head-up tilt resulted in a 25% fall in systolic blood pressure without causing any symptoms of cerebral hypoperfusion. After resting supine for 30 min a catheter was inserted in a forearm vein. The tetraplegics were tilted to the predetermined angle (between 30 and 45°) and the normal controls to 45°. This position was maintained for 30 min, during which time pulse and blood pressure were recorded at 5-min intervals. Blood was also taken at 5-min intervals for subsequent estimation of haematocrit and plasma AVP.

AVP Infusion

Following the head-up tilt and after resting supine for 30 min a catheter was inserted in a vein in the other forearm. All subjects received incremental 5-min infusions of AVP at 0.05, 0.2, 0.5 and 2.0 pmol/kg/min. At 5-min intervals pulse and blood pressure were recorded and blood drawn for subsequent measurement of plasma AVP. Blood samples were collected into lithium heparin or potassium EDTA tubes and immediately put on ice. The lithium heparin tubes were centrifuged at

3000 r.p.m. at 4° C and the separated plasma used to measure sodium (flame photometer) and osmolality (Osmomat 030, Gonotec, Berlin, FRG). Haematocrit was measured after microcentrifugation (Hawkesley microcentrifuge). Plasma was stored for less than one month at −20° C before subsequent Sep-Pak extraction and estimation of AVP by radioimmunoassay (Williams *et al.*, 1985*a*). The detection limit for the assay was 0.25 fmol/tube. The coefficients of variation for control AVP samples (2 fmol) were 6% (intra-assay) and 17% (interassay).

Mean arterial pressure (MAP) was calculated by adding one-third of the pulse pressure to the diastolic pressure. Basal heart rate and blood pressure were taken as the mean of 3 consecutive readings while supine. Results were expressed as mean ±SEM. The significance of changes was assessed by two-way analysis of variance and comparisons between the two groups of subjects was made using Duncan's multiple comparison test. P values > 0.05 were taken as being not significant (n.s.).

TABLE CHANGES IN PLASMA OSMOLALITY DURING INTRAVENOUS INFUSION OF HYPERTONIC SALINE IN CONTROL SUBJECTS AND IN TETRAPLEGICS

	Controls		*Tetraplegics*	
Time (min)	*Na^+ (mmol)*	*Osmolality (mosmol/kg)*	*Na^+ (mmol)*	*Osmolality (mosmol/kg)*
0	141±1.1	289±1.2	140±0.6	286±1.4
30	143±1.0	295±1.0	142±0.5	290±0.5
60	145±0.9	296±1.2	144±0.6	295±0.8
90	145±0.6	299±1.4	146±0.7	298±0.7
120	146±0.7	302±1.6	149±0.6	303±1.0

RESULTS

Hypertonic Saline Infusion

The changes in osmolality (*see* Table) were associated with a significant rise in plasma AVP ($P < 0.01$) in both the controls and the tetraplegics (fig. 1). Plasma levels of AVP in the tetraplegics reached 7.1±1.0 pmol/l compared with 4.5±1.0 pmol/l in the controls but this difference was not statistically significant.

In the control group there was a small but insignificant rise in MAP (from 79±2.5 mmHg at the onset to 84±3.2 mmHg at the end of the infusion) and heart rate (from 56±4.0 to 59±3.8 beats/min) (fig. 1). The tetraplegic group, however, showed an increase in MAP from 87±5.3 to 101±5.2 mmHg ($P < 0.05$). This rise was significantly greater than that in the control group both at 90 ($P < 0.05$) and 120 min ($P < 0.05$) but was not associated with any significant change in heart rate (73±5.9 beats/min at onset and 70±4.8 beats/min at end of infusion).

Head-up Tilt

In the control subjects, 45° head-up tilt was not associated with any significant change of MAP but heart rate rose from 67±0.9 at rest to a maximum of 82±2.3

($P < 0.01$) (fig. 2). In the tetraplegics MAP fell by 16 mmHg at 5 min and remained between 17 and 22 mmHg below basal values for the duration of the tilt (fig. 2). Heart rate rose from 73±7.2 at rest to a maximum of 83±6.4 at 10 min (n.s.). Haematocrit in the controls rose from 41.7±1.2% at rest to 43.5±1.1% at 30 min ($P < 0.05$) and in the tetraplegics from 40.8±1.9% to 41.7±2.3%, respectively (n.s.).

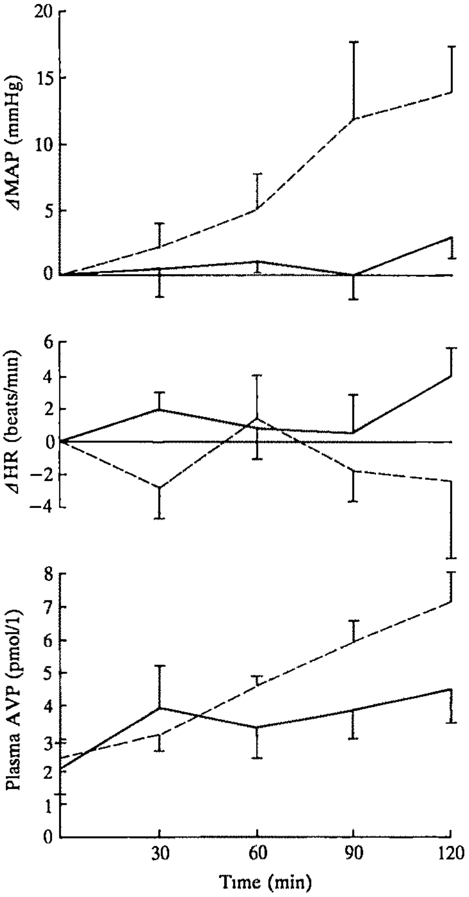

Fig. 1. Changes in mean arterial pressure (MAP), heart rate (HR) and plasma AVP during intravenous infusion of 0.85 M saline at 0.05 ml/kg/min over 2 h in controls (solid line) and tetraplegics (broken line). Mean±SEM; n = 6 in each group.

Plasma AVP rose from 1.2±0.23 pmol/l at rest to 2.1±0.38 pmol/l at 30 min ($P < 0.05$) in the controls and from 1.8±0.43 to 5.5±1.46 pmol/l ($P < 0.05$) in the tetraplegics. The rise in AVP in the tetraplegics was significantly greater than that found in the normal controls ($P < 0.05$). There was no significant difference in resting levels of AVP between the two groups.

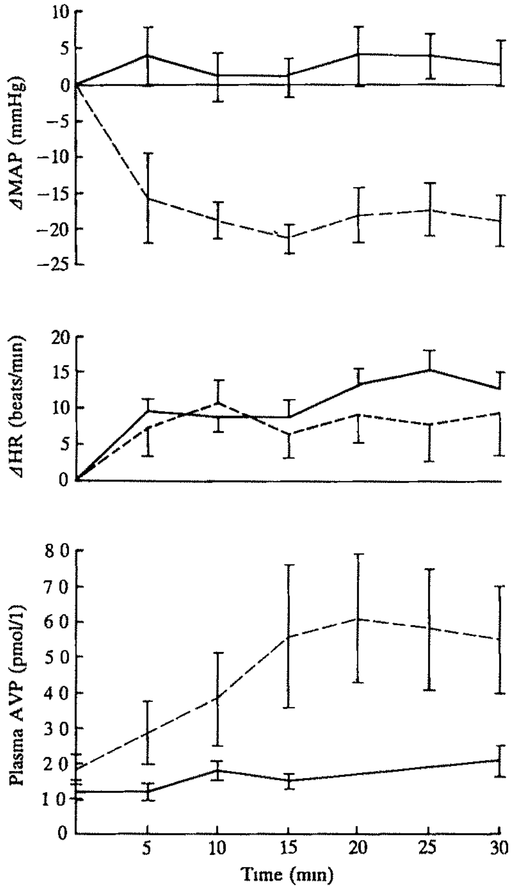

FIG. 2. Changes in mean arterial pressure (MAP), heart rate (HR) and plasma AVP during head-up tilt over 30 min in controls (solid line, n = 6) and tetraplegics (broken line, n = 8). Mean ± SEM.

AVP Infusion

The rise in plasma AVP concentration was similar in both the controls and the tetraplegics in response to AVP infusion (fig. 3). This rise was not associated with any significant change in either MAP or heart rate in the normal controls whereas in the tetraplegics MAP rose markedly in response to AVP, by 13.7 ± 3.1 mmHg at an infusion rate of 0.5 pmol/kg/min ($P < 0.01$) and by 15.3 ± 3.2 mmHg at 2.0 pmol/kg/min ($P < 0.01$) (fig. 3). This was associated with a fall in heart rate from 71 ± 6.5 to 62 ± 7.0 beats/min ($P < 0.01$).

DISCUSSION

The results of this study indicate that tetraplegics have appropriate cardiovascular and osmotic control of AVP secretion. The release of AVP in response to

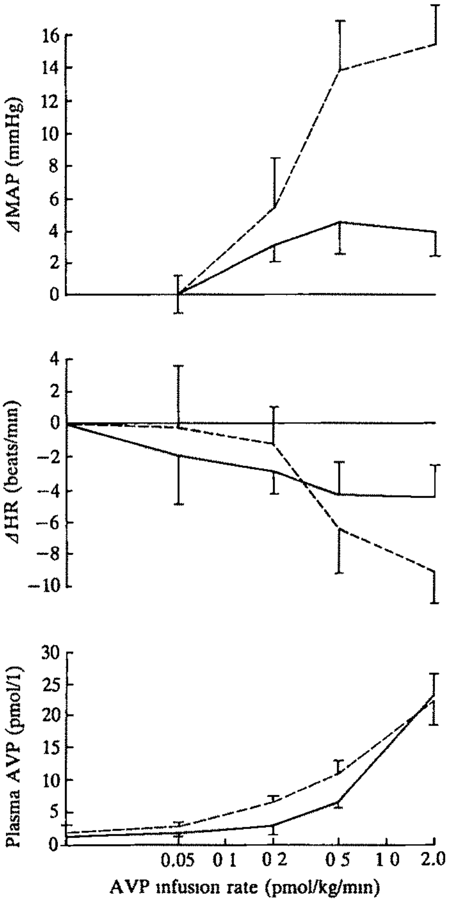

FIG. 3. Changes in mean arterial pressure (MAP), heart rate (HR) and plasma AVP during incremental 5-min intravenous infusions of AVP in controls (solid line) and tetraplegics (broken line). Mean ± SEM; n = 6 in each group.

hypertonic saline was not significantly different from that of control subjects. The release of AVP in response to head-up tilt was increased commensurate with the simultaneous fall in blood pressure due to their loss of sympathetic vasomotor control. The latter results are similar to those reported by Sved *et al.* (1985). This increased postural release of AVP may be an important cause of the oliguria often seen in patients with spinal cord transection during long periods of sitting, especially since glomerular filtration rate has been found not to fall with head-up tilt in these patients (Ragnarsson *et al.*, 1981). Bladder ultrasound or catheterization often reveals an empty or near empty bladder in these patients (H.L.F., personal observation), an undesirable situation in patients already prone to recurrent urinary tract infections, bladder calculi and chronic renal failure.

Although AVP is an extremely potent vasoconstrictor, its role in blood pressure control is controversial. In dogs, infusion of AVP causes an increase in MAP and a decrease in heart rate, the effect on MAP being increased after sino-aortic denervation (Cowley *et al.*, 1974; Montani, 1980). Conscious rats also show a pressor and bradycardic response to AVP (Möhring *et al.*, 1981) with enhancement of pressor sensitivity to AVP following ganglion blockade (Matsuguchi and Schmid, 1982). These studies and others suggest that the pressor response to AVP in these two species is moderated by baroreflex responses. There is, however, great interspecies variation in response to AVP (Bennett and Gardiner, 1986). Most studies in man report that infused AVP has either no, or only transient, pressor effects and so only minor baroreceptor activation as evidenced by decreased heart rate (Graybiel and Glendy, 1941; Simpson *et al.*, 1986; Williams *et al.*, 1986*a*). To complicate matters further, if a selective V_2 AVP agonist is infused, MAP actually falls (Williams *et al.*, 1986*b*).

Increased sensitivity to the pressor response of AVP in patients with PAF has been reported (Williams *et al.*, 1986*a*). Because of the presence of both peripheral and central lesions in the autonomic nervous system of these patients it is uncertain whether their increased sensitivity to AVP represents a change in activity of central pathways mediating baroreceptor reflexes or whether the autonomic neuropathy itself results in changed sensitivity to AVP.

In the present study we have looked at tetraplegic subjects who have normal ninth and tenth cranial nerve function and normal central pathways, but an isolated sympathetic and sacral parasympathetic outflow. Tetraplegics are known to have an increased pressor response with bradycardia to infused noradrenaline (Mathias *et al.*, 1976) but, unlike subjects with progressive autonomic failure, they show a significant bradycardic response to AVP, presumably mediated via the baroreflex and intact vagal outflow. In addition they show a marked pressor response to AVP at plasma levels within the physiological range, quite unlike their normal controls. Clearly the difference in pressor response to AVP between controls and tetraplegics cannot be ascribed to a loss of baroreceptor function. It could represent an increase in sensitivity to the pressor vascular effects of AVP; alternatively, it may reflect a failure of the baroreflex-mediated changes in sympathetic tone in response to AVP. The increased bradycardic effect of the AVP infusion in the tetraplegics compared with controls is probably the result of baroreflex activation secondary to the marked pressor effect.

There is evidence of differential effects of AVP on different arteries (Monos *et al.*, 1978) and it is possible that sympathetic denervation, whether due to cervical spinal cord transection, progressive autonomic failure or other causes, results in local changes in AVP receptor sensitivity. This may be a supersensitivity phenomenon, a change in the ratio of V_1 to V_2 receptors or even a change in the importance of different vascular beds in blood pressure control after sympathetic denervation. It is interesting to speculate whether the increased pressor response to AVP plays any role in tetraplegics such as preventing them from excessive postural hypotension. Certainly the plasma levels of AVP reached during head-up tilt (6.1 ± 1.8) and hypertonic saline infusion (7.1 ± 1.0) are in the range associated with a pressor effect during the AVP infusion.

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NEUROHYPOPHYSEAL PEPTIDE FUNCTION DURING EARLY POSTOPERATIVE DIABETES INSIPIDUS

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SUMMARY

Neurohypophyseal function has been investigated in 11 children undergoing pituitary or suprasellar surgery. All had corticosteroid and thyroxine replacement; 9 developed diabetes insipidus (DI) within 1–12 h of operation. At the onset of DI, the plasma vasopressin (AVP) concentration was 3.9 ± 1.2 pmol/l, considerably higher values usually associated with cranial DI (< 0.9 pmol/l). AVP fell significantly to 1.1 ± 0.2 pmol/l by the second day of DI. There was a similar change of levels of the AVP prohormone/carrier peptide, neurophysin I, but plasma oxytocin did not change significantly. High performance liquid chromatography of plasma at the onset of DI revealed a major peak that coeluted with synthetic AVP and two smaller peaks of AVP immunoreactivity. Seven patients required very large doses of desamino-8-D-arginine vasopressin (DDAVP) during the first day; 4 needed smaller doses on day 2. Water deprivation tests were performed on days 6 and 14 after operation in 5 patients with prolonged DI (2 with a triple response). There were no differences in plasma AVP on the two occasions but urinary AVP excretion rate was significantly higher on day 6 (2.4 ± 0.8 pmol/h) than day 14 (0.7 ± 0.3 pmol/h). It is concluded that early postoperative DI is not due to decreased levels of circulating AVP but may be related to the release of biologically inactive precursors from the damaged neurohypophysis. These may lead to renal refractoriness to AVP. There is a higher urinary AVP excretion rate on day 6 than day 14 after operation in both patients with a triple response and those with uninterrupted DI. Other factors may determine whether or not a transient resolution phase of DI occurs.

INTRODUCTION

Cranial diabetes insipidus (DI) may occur following surgery to the pituitary or hypothalamus (Randall *et al.*, 1960) and exhibits one of three patterns (Verbalis *et al.*, 1985). (1) Transient DI. The polyuria is of abrupt onset usually within the first 24 h of operation and resolves over several days. This form is particularly associated with intrasellar surgery. (2) Prolonged or permanent DI. Again the onset is early and rapid but the disorder persists for weeks or may be permanent. This pattern is associated with more proximal damage to the neurohypophyseal stalk

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or hypothalamus. (3) Triple response. Following a similar early onset of DI there is a transient remission from polyuria (interphase) lasting a few days until prolonged DI recurs (Ikkos *et al.*, 1955; Verbalis *et al.*, 1985). The resolution phase may be only partial or may even involve a frank syndrome of inappropriate antidiuresis (Lipsett *et al.*, 1956) and is thought to be due to nonspecific release of arginine vasopressin (AVP) from damaged neurohypophyseal tissue degenerating in situ (Hollinshead, 1964; László and de Wied, 1966).

Although the various phases of postoperative DI should be associated with altered concentrations of plasma AVP there is little experimental evidence for such changes (Cusick *et al.*, 1984; Verbalis *et al.*, 1985). Marked variations in the levels of the AVP prohormone/carrier-peptide human neurophysin I (HNPI), or of the other neurohypophyseal nonapeptide hormone oxytocin (OT), have not been demonstrated during the phases of the triple response (Verbalis *et al.*, 1985).

We have investigated the neurohypophyseal peptides arginine vasopressin, human neurophysin I and oxytocin during the early postoperative period in children undergoing pituitary and suprasellar surgery.

METHODS

Patients

Eleven children aged 1 yr 10 months to 15 yrs (median 8 yrs) were investigated. All had operations on the hypothalamus or pituitary: 9 had craniopharyngiomas, 1 had an optic nerve glioma (biopsy only) and 1 had a pituitary adenoma with Cushing's disease (Table). All had preoperative pituitary function tests. Informed consent was obtained from the patients and/or their parents.

Protocol

Blood samples were obtained at the onset of polyuria following surgery, prior to antidiuretic therapy, and 24 h after the start of DI. Urine output was measured and replaced hourly for 72 h

TABLE CLINICAL DETAILS FROM 11 PATIENTS UNDERGOING NEUROHYPOPHYSEAL SURGERY

Sex	*Age (yrs)*	*Diagnosis*	*Onset of DI* (h)	*Outcome*
F	9	Cp	9	Triple response
M	22 months	Cp	3	Prolonged DI
M	11	Cp	10	Prolonged DI
F	10	Glioma	—	Normal water balance throughout
M	15	Adenoma	7	Transient DI
F	4	Cp	12	Triple response
M	3½	Cp	4	Initial DI; died, CVS collapse
M	8	Cp	8	Triple response
M	3	Cp	—	Normal water balance throughout
M	7	Cp	5	Prolonged DI
M	15	Cp	1	Initial DI; died of SAH

Cp = craniopharyngioma, Glioma = optic glioma biopsy; Adenoma = pituitary tumour with Cushing's disease, SAH = subarachnoid haemorrhage.

and then daily thereafter. An aliquot was retained for analysis. Patients with abnormal postoperative fluid balance had a water deprivation test performed on day 6 or at the onset of any remission phase of the DI. A further water deprivation test was performed at the end of the second week (mean, day 14; range, day 13–15 following operation). Antidiuretic therapy was discontinued at least 18 h and usually 24 h before fluid deprivation. Blood samples were obtained at the beginning and end of the test. The test was terminated after 7 h or when 3% of body weight had been lost. All urine passed during the test was timed and collected for volume estimation and analysis.

Postoperative DI was established by the presence of hypotonic polyuria (> 2 ml/kg/h) with concurrent plasma hyperosmolality (> 300 mosmol/kg in the absence of hyperglycaemia or hyperuricaemia) or hypernatraemia (> 143 mmol/l). Two subjects were treated with antidiuretic agents because of hypotonic polyuria and rising plasma osmolality before having achieved the above criteria. They were included in the postoperative DI analysis since both showed marked cranial DI on formal water deprivation testing on the sixth day after operation.

All patients were given prophylactic corticosteroid replacement during and after operation, (dexamethasone 0.5–2 mg 6–8 hourly, depending on body weight). Thyroid function was normal or adequately replaced before operation and was routinely replaced from the second postoperative day until testing of pituitary function was performed. The specific AVP (V_2) analogue desamino-8-D-arginine vasopressin (DDAVP) was used as the antidiuretic agent. It was administered parenterally in doses of 0.4 μg. Subsequent doses of DDAVP were not given until hypotonic polyuria had recurred.

Samples

Blood was taken at venepuncture and the plasma separated in a chilled centrifuge at 4 °C within 30 min of collection. Electrolytes were measured by flame photometry and osmolality by freezing point depression. The remaining plasma and urine were frozen at −20 °C prior to peptide assay. Sufficient plasma was obtained from 5 patients to allow complete peptide analysis. AVP was estimated in all patients. Plasma samples for AVP, OT and HNPI were extracted through octadecasilyl silica cartridges (Sep-pak, Waters, Mass) Extraction yield was > 90% for both AVP and OT. AVP and OT were measured in sensitive and specific radioimmunoassays (Williams *et al.*, 1985). Urine was assayed unextracted. All specimens from each subject were estimated in the same assay. Intra-assay coefficients of variation (CV) were < 5% for both AVP and OT (2 fmol/tube, 10 replicates). Inter-assay CV was 15% for AVP and 10% for OT (2 fmol standards). Cross-reactivity with DDAVP was less than 0.1%. Detection limits were 0.4 pmol/l for plasma AVP and OT and 2.5 pmol/l for urinary AVP. Patients with cranial DI usually have plasma AVP values below 0.9 pmol/l. HNPI was measured by radioimmunoassay (Burford and Robinson, 1982). All samples were measured in the same assay (CV 10%). The detection limit was 0.05 ng/ml. Values less than 0.02 ng/ml are usually associated with cranial DI in man (Pullan *et al.*, 1979).

High performance liquid chromatography (HPLC) was performed on plasma taken at the onset of DI from 1 patient with a triple response. It was not felt justifiable to take the large volumes of blood necessary for this analysis from all the children. The plasma was extracted as above and loaded on to a reverse-phase column (Nucleosil C8). Fractions were collected from a linear gradient of 12% to 48% acetonitrile in 0.1% trifluoroacetic acid. The fractions were assayed for AVP as above with a minimum detectable concentration of 0.15 fmol/fraction. HPLC of normal human plasma parallels synthetic AVP. Both show a single major peak of immunoreactivity at fractions 26 to 27 with a short 'tail' of minor peaks in subsequent fractions. Neither yield AVP immunoreactivity in fractions 16 or 42.

Statistics

Differences between peptide concentrations were assessed using paired t tests. Statistical significance was set at $P < 0.05$. Values are means ± SE.

RESULTS

Two patients had normal water balance following operation; 1 had an optic glioma biopsy, the other a craniopharyngioma. The data from these subjects were excluded from the analysis.

Nine patients developed early postoperative DI. The onset of DI occurred between 1 and 12 h (mean 6.6 h) following the end of the operation (Table). The plasma osmolality at the onset of DI was 304.9±3.4 mosmol/kg. At this time plasma AVP was high at 3.9±1.2 pmol/l. By day 2, plasma AVP had fallen significantly to 1.1±0.2 pmol/l ($P < 0.05$). HNPI was also initially elevated at 0.7±0.2 ng/ml and fell significantly to 0.2±0.1 ng/ml by the second day ($P <$ 0.05) (fig. 1).

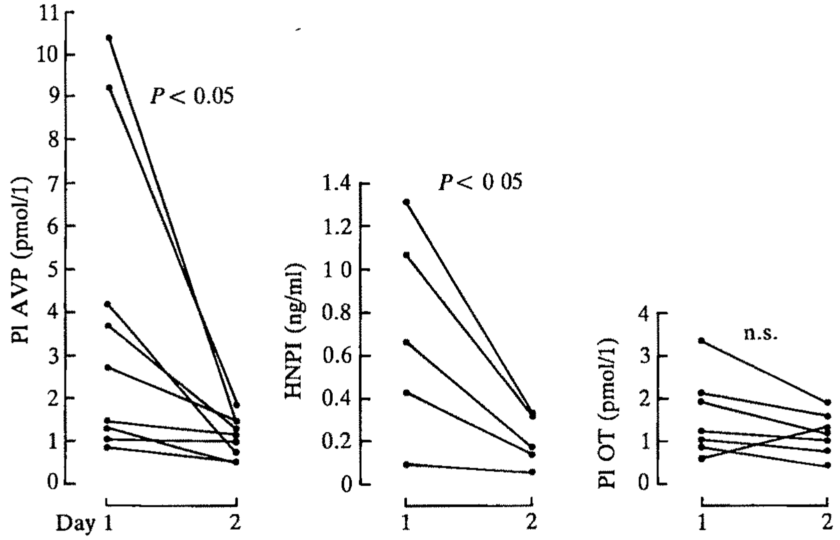

FIG. 1. Changes in plasma vasopressin (Pl AVP), human neurophysin I (HNPI) and plasma oxytocin (Pl OT) during the first 2 days following the onset of postoperative diabetes insipidus in children.

Plasma oxytocin showed no significant change between the first (1.8±0.4 pmol/l) and second postoperative days (1.2±0.1 pmol/l), remaining within the normal range (0.8–3.5 pmol/l). Indeed 1 patient with prolonged DI and a triple response had a marked rise in OT between the first and second days.

DDAVP

Patients with DI responded with an antidiuresis when treated with parenteral DDAVP (0.4 μg doses); 4 out of 7 patients required 3 or more doses within the first 24 h because of recurrent polyuria. None needed more than 1 dose on the second day.

Two patients died within 48 h of operation. Both had craniopharyngiomas and showed early DI. One developed marked instability of blood pressure, heart rate and temperature regulation associated with late hyperglycaemia. DI began 3 h after operation and was difficult to control. Death occurred 25 h after operation and was related to cardiorespiratory collapse. The second patient had a good initial course, although DI started only 1 h after operation, but deteriorated 16 h after surgery. A CT scan revealed a subarachnoid haemorrhage. Despite therapy the patient deteriorated further and died 47 h after operation.

Of the remaining 7 patients, 1 developed transient DI with partial cranial DI at day 6 and normal water regulation thereafter. Three exhibited a triple response with an interphase requiring no antidiuretic therapy (frank inappropriate antidiuresis in 1 and urinary concentration off antidiuretic therapy in the remainder). The onset of increased urine osmolality occurred during the fourth and fifth post-surgical days and lasted 2 to 5 days. The highest urine osmolalities achieved during remission and without DDAVP therapy were 1024, 350 and 466 mosmol/kg. All 3 relapsed to complete DI after remission. The remaining 3 patients appeared to have prolonged DI after onset, without clinical evidence of remission or amelioration.

Five patients (2 with a triple response, 3 with uninterrupted DI) had water deprivation tests on days 6 and 14 following surgery. All but one of the tests showed increases in urine osmolality of less than 50 mosmol/kg. One patient with a triple response interphase showed an increase in urinary osmolality of 262 mosmol/kg during water deprivation on day 6 but no increase on day 14. The results from all 5 patients were pooled for further analysis (fig. 2). There was no apparent difference in measurements other than urine osmolality between patients with a triple response and those with uninterrupted DI.

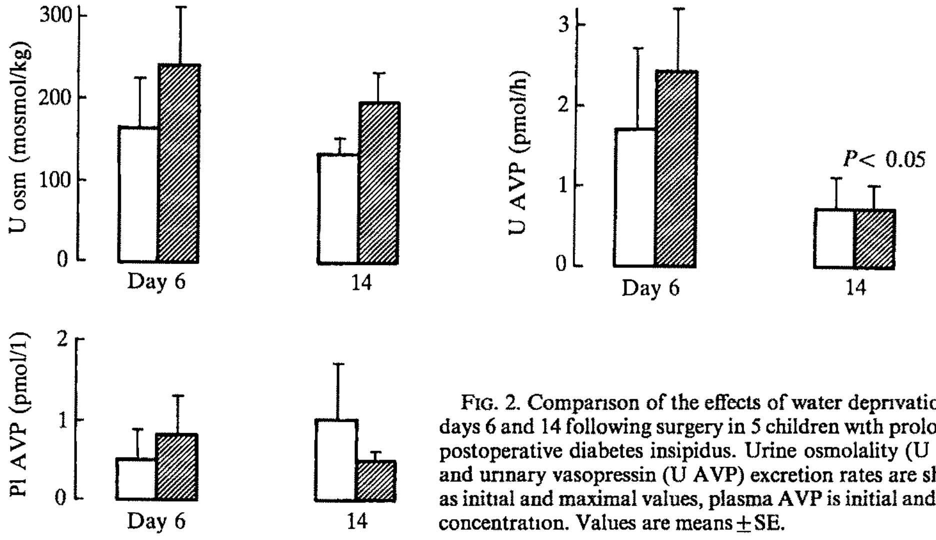

FIG. 2. Comparison of the effects of water deprivation on days 6 and 14 following surgery in 5 children with prolonged postoperative diabetes insipidus. Urine osmolality (U osm) and urinary vasopressin (U AVP) excretion rates are shown as initial and maximal values, plasma AVP is initial and final concentration. Values are means ± SE.

There were small statistically insignificant changes in plasma AVP during the water deprivation tests on days 6 and 14. The final plasma AVP achieved was similar on both occasions (fig. 2). There were no changes in plasma OT levels (1.2 ± 0.1 pmol/l, day 6; 1.1 ± 0.4 pmol/l, day 14).

The maximal urinary AVP excretion rate was significantly higher during the water deprivation test on day 6 (2.4 ± 0.8 pmol/h) than during the test at the end of the second week (0.7 ± 0.3 pmol/h), $P < 0.05$, (fig. 2). There was no apparent difference in urinary AVP excretion on day 6 between patients with a triple response interphase and those without evidence of remission of DI.

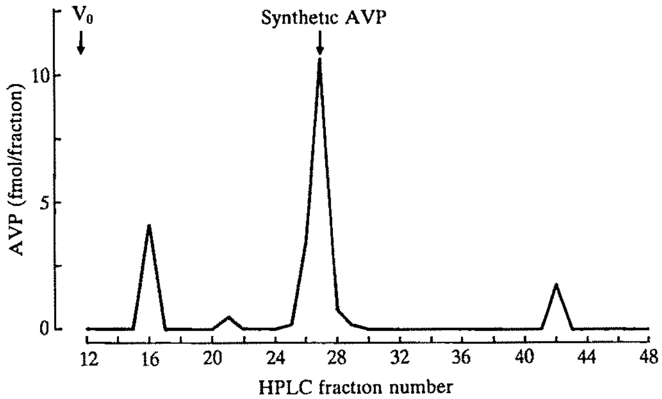

FIG 3. HPLC (redrawn) of plasma from a patient at the onset of postoperative diabetes insipidus Radioimmunoassay of fractions for vasopressin (AVP). V_0 = void volume.

HPLC

HPLC analysis of plasma from 1 patient at the onset of DI revealed a major peak (> 70%) of AVP immunoreactivity that coeluted with standard AVP. There were two smaller peaks of immunoreactivity that were separate from standard AVP (fig. 3). An aliquot of extracted plasma, assayed with the HPLC fractions, gave a similar plasma AVP value to that obtained in the original assay.

DISCUSSION

Diabetes insipidus (DI) occurred in approximately 80% of our cases. This is comparable with larger published series of surgery for childhood craniopharyngiomas (9 out of 11 of our cases) which have suggested an incidence of 70 to 74% (Thomsett *et al.*, 1980; Newman *et al.*, 1981; Lyen and Grant, 1982). These were all retrospective analyses and would probably have underestimated the incidence of transient DI.

All patients with postoperative DI had an abrupt onset of polyuria within 24 h of surgery. The results clearly demonstrate high plasma immunoreactive AVP concentrations during the initial DI, at levels usually associated with maximal antidiuresis. AVP fell significantly during the next 24 h, but remained above the concentrations typically found in cranial DI (< 0.9 pmol/l) until the end of the first postoperative week. The high values of plasma AVP, and their subsequent fall, were confirmed by parallel changes in levels of the AVP prohormone/carrier peptide, HNPI, which also remained above the concentrations usually associated with cranial DI (Pullan *et al.*, 1979).

Previous work has concentrated on plasma levels of AVP after the first day following operation (Verbalis *et al.*, 1985) and the abrupt onset of DI common to all three patterns of postoperative DI has not been evaluated, but simply ascribed to 'pituitary bruising' (Lipsett *et al.*, 1956). Although the high postoperative levels of AVP demonstrated may be a result of surgery and anaesthesia, the association of these values with the onset of polyuria is unusual. The DI might therefore be secondary either to renal unresponsiveness to circulating AVP or to the release of immunoreactive forms of AVP which lack biological activity. AVP is synthesized as a pre-prohormone in the magnocellular neurons of the paraventricular and supraoptic hypothalamus. This then undergoes processing during axonal transport before storage and secretion from neurohypophyseal terminals (Gainer, 1983). Surgical interruption of the neurohypophyseal tract might allow partially processed precursors without biological activity to enter the circulation. Similar larger molecular weight immunoreactive forms have been demonstrated in normal tissue (Kasson *et al.*, 1985) and with ectopic hormone production by a pulmonary tumour (Smitz *et al.*, 1985). However, our HPLC results suggest that, in 1 patient at least, the major immunologically-recognized form is authentic AVP. In this patient the abrupt onset of postoperative DI does not appear to be due to insufficient circulating AVP.

An alternative mechanism for immediate postoperative DI could be renal refractoriness to AVP. This is unlikely to be mediated by nonspecific effects, such as changes in sympathetic tone following surgery, since cranial DI does not commonly occur following other neurosurgical procedures. More specific renal insensitivity might be due to receptor blockade by AVP-like precursor peptides released by the damaged neurohypophysis. The HPLC study revealed two peaks of AVP immunoreactivity which did not coelute with synthetic AVP and may represent such biologically inactive precursors. Other substances without either immunological or biological activity might also be present. Binding of inactive forms to AVP receptors might be expected to be reversed by high doses of the agonist. Parenteral DDAVP therapy led to an antidiuresis in all cases but the very large doses used had to be repeated at least twice within 24 h in more than half of the subjects. This suggests that there was some renal refractoriness to this renal (V_2) specific AVP analogue and lends support to the hypothesis that inactive AVP-like peptides might contribute to the abrupt and early onset of postoperative DI. An alternative explanation for the occurrence of DI in the presence of adequate circulating AVP in these patients may be down-regulation of renal AVP receptors following much higher levels of AVP released during operation. However, in 2 patients where preoperative samples were taken, plasma AVP concentrations during surgery were similar to the levels at the onset of DI. In addition, although AVP has a short plasma half-life, DI has not been described following AVP infusions to plasma levels in great excess of those found in this study.

OT levels fell slightly after surgery and remained stable thereafter, confirming the limited previous data (Verbalis *et al.*, 1985). This failure to parallel the changes in plasma AVP might be due to differences in the hypothalamic control mechanisms for the two hormones. Alternatively, our assay may not detect any precursors of OT released following surgery.

Of the 6 patients who developed prolonged DI, 3 had a triple response. There was no evidence of any differences in plasma or urinary AVP between patients with uninterrupted DI and those with a phase of remission. There was little urinary concentration or plasma AVP response to water deprivation during the phase of remission of DI in subjects with a triple response or at the equivalent time in patients with uninterrupted prolonged DI. This supports the nonspecific nature of the remission phase which has been clearly shown to be due to in situ degeneration of neurohypophyseal tissue in animals (Hollinshead, 1964).

Although previous studies have failed to show any differences in AVP levels during the various phases of postoperative DI in man (Verbalis *et al.*, 1985), and there were no significant variations in plasma AVP in this investigation, we have demonstrated a significant fall in urinary AVP excretion between days 6 and 14. This occurred in patients with prolonged DI, regardless of any clinical evidence of a triple response. Although caution should be exercised when interpreting urinary AVP estimations because of the small fraction of filtered AVP that is excreted (Robertson, 1977) and the presence of non-AVP immunoreactivity in urine (Claybaugh and Sato, 1985), changes occurring with time in the same patient are likely to be a genuine representation of alterations in the secretion of the peptide (Miller and Moses, 1972). In addition, very low dose AVP infusions led to an increase in both urinary osmolality and AVP excretion rate without alteration of plasma AVP levels (Dixey *et al.*, 1986). These results provide the first evidence of any neurohormonal difference between the phases of postoperative DI in man. A similar finding has been described in postsurgical DI in rats using a bioassay of urinary antidiuretic activity (Lászlό and de Wied, 1966). Since the urinary AVP excretion rate also changed in patients with uninterrupted DI, other factors are likely to be involved in determining whether urinary concentration occurs or not. These might include increased renal sensitivity to AVP, similar to that described in hereditary cranial DI (Block *et al.*, 1981), or the secretion of biologically inactive and immunologically unrecognized antidiuretic peptides from the damaged neurohypophysis. Urinary concentration mechanisms unrelated to AVP have also been described (Berliner and Davidson, 1957), but the very large falls in glomerular filtration rate necessary for modest urinary concentration are unlikely to have occurred in these patients.

Two of our patients died within 48 h of surgery. In 1 the cause of death was presumed to be related to widespread hypothalamic damage. The second death was probably due to a subarachnoid haemorrhage, a complication that has been previously reported in a similar patient (Lyen and Grant, 1982). Both deaths were associated with a very early onset (1 and 3 h) of postoperative DI. This was due, presumably, to substantial hypothalamic damage and might be an important indicator of high-risk postsurgical cases.

In summary, we provide evidence that the abrupt onset of postoperative DI is not associated with low plasma AVP levels, but may be related to release of biologically inactive precursors from the damaged neurohypophysis. In patients with prolonged postoperative DI, with and without a triple response, there is a higher urinary AVP excretion rate during the first than the second week after surgery. Other factors must be involved to determine whether DI shows a transient remission phase or is uninterrupted.

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RECOVERY FROM IDEOMOTOR APRAXIA

A STUDY ON ACUTE STROKE PATIENTS

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SUMMARY

In this study we investigated whether there are predictors for recovery from ideomotor apraxia (IMA) in patients with focal left hemisphere vascular lesions. Recovery was followed in 26 patients, first examined between 15 and 30 days postonset. They were apraxic at the first examination and had a second (and in some cases, a third) neuropsychological assessment after some months. Six patients with bilateral lesions were also studied to help to define the role of the right hemisphere in recovery from IMA. Other neuropsychological variables (Token Test, Progressive Matrices and Oral Apraxia scores) and site and size of the lesion were also determined. The main results are that (1) improvement from IMA is related to the site of the lesion (anterior lesions faring better); (2) the evolution of IMA is related more to the evolution of oral apraxia than to the evolution of other neuropsychological variables; and (3) the presence of a second lesion in the right hemisphere did not have the negative influence on recovery that might have been expected.

INTRODUCTION

Apraxia is a common sequel to a left hemisphere lesion and is particularly frequent in aphasia. Our understanding of apraxia and of the neural mechanisms that underly it is still mainly based on the classical single case studies. Recently, however, apraxia has attracted much attention and has been approached from several points of view. Many studies have been devoted to the kind of gestures that are deranged in ideomotor apraxia (IMA), to the location of the lesions that produce it, and to such questions as the incidence of IMA in patients with left hemisphere damage and its association with aphasia, and whether they coexist because of anatomical proximity of the respective crucial neural areas or because they use the same anatomical structure and are simply different expressions of an underlying common mechanism (Kimura, 1976, 1982; Mateer and Kimura, 1977).

The bulk of interest has been focused on the initial state of apraxia, mainly as to the site of the lesion and the relationship of IMA to aphasia. Much less is known about the natural course of IMA. Apraxia is usually defined as impairment in the ability to carry out purposeful or intentional movements, implying that these movements can be carried out automatically when they are invoked by the situation, such as crossing oneself when entering a church. This dissociation between

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automatic and intentional movements probably explains the lack of interest in recovery from apraxia, since apraxia is only rarely a handicap in everyday life.

The present investigation was undertaken to study the evolution of IMA. Its two purposes were to assess (1) whether there is any significant evolution of IMA and whether variables capable of predicting it can be identified; and (2) what is the role of a concurrent lesion in the right hemisphere in the evolution of IMA.

MATERIAL AND METHODS

Subjects

Records of 767 patients seen in the Aphasia Unit of Milan University Neurological Clinic between March 1979 and August 1983 were reviewed. Patients conforming to the following conditions were selected for further study: (1) right-handedness according to the Edinburgh Inventory (minimum score 9/12; Oldfield, 1971); (2) no previous cerebral lesion; (3) a left-sided vascular lesion ascertained by clinical evidence and CT scan; (4) a language and neuropsychological evaluation between 15 and 30 days after the stroke; (5) the presence of apraxia on first examination; and (6) a second neuropsychological examination after at least five months. Twenty-six acute patients, 19 male and 7 female (mean age 56.7 ± 12.3 yrs; mean education 6.9 ± 2.7 yrs) with a mean interval between the first and second assessments of 8.2 ± 4.2 months, range 5–23 months, fulfilled these conditions. Factors influencing the evolution of IMA were investigated in this group.

From the original continuous series we also selected 25 not necessarily acute right-handed vascular patients with bilateral focal lesions ascertained by CT scan, the right hemisphere lesion having preceded or accompanied that on the left. Eight of the 13 patients in this group who were apraxic at the first examination were given a second neuropsychological assessment at least five months after the first and they provided information as to IMA evolution in bilaterally damaged patients. None of these patients had a left hemiparesis or hemianaesthesia at the time of examination: Case B6 had had a clinically evident left hemiparesis two years before testing.

Tests and Procedures

Ideomotor apraxia. This was evaluated with a 24-item test (De Renzi *et al.*, 1980) consisting of movements of the whole arm and hand or fingers, single or in sequence, meaningful or meaningless, which the patient had to imitate with the hand ipsilateral to the lesion. Patients with bilateral lesions also performed the test with their left arm. If the patient's first performance was not correct, a second and a third example of the same item were presented. Scores ranged from 0 to 3 for each item depending on whether the patient was never correct or if he succeeded on the third, second or first presentation. The cut-off score was 53 out of a maximum score of 72 (De Renzi *et al.*, 1982).

Oral apraxia. This was evaluated with a 10-item test requiring the execution of movements of the buccofacial musculature. The cut-off score was 16/20 (De Renzi *et al.*, 1968).

Raven's Coloured Progressive Matrices (CPM). This test was administered with a time limit of 10 min (Basso *et al.*, 1973).

Token Test. A shortened version of the Token Test with 36 items and a cut-off score for normals of 29 correct responses (De Renzi and Faglioni, 1978) was employed.

Aphasia testing. Aphasia was assessed with the Standard Language Examination currently in use in our Aphasia Unit (Basso *et al.*, 1979). On the basis of the Token Test score and the Standard Language Examination, patients were divided according to presence/absence and severity of aphasia, and the type of the disorder along the fluency/nonfluency dimension which considered phrase length, rate of speech, articulatory disorders and melodic line. One patient was classified as nonaphasic, 10 as fluent aphasic and 13 as nonfluent aphasic. Two patients could not be classified as fluent or nonfluent with certainty.

CT scan. All patients had CT scans without enhancement. The lesions were mapped onto lateral diagrams as proposed by Luzzatti *et al.* (1979). The corticosubcortical lesions were also subdivided according to size. A 'large' lesion involved more than 20% of the area of the standardized lateral diagram of the convexity of the hemisphere and a 'small' lesion 20% or less. The lesion in 1 patient could not be mapped because of artefact. Another two lesions were not reconstructed onto lateral diagrams because they were *entirely* deep.

RESULTS

Variables Related to Recovery from IMA

The improvement on second examination was highly significant (Table 1). Separating the sample according to the median severity at onset (i.e., 35), both groups were found to have improved significantly. We assessed whether some factors have differential effects on the outcome in the two groups by dividing the sample into those with improvement above or below the *median* (i.e., 14). Sex, type of aphasia (fluent/nonfluent), lesion size ('small' or 'large') and language rehabilitation were all not significantly related to recovery, each yielding a χ^2 value of < 1. The same applied to continuous variables such as age ($F(1, 24) < 1$, n.s.), education ($F(1, 24) = 1.485$, n.s.) and initial severity ($F(1, 24) = 1.897$, n.s.), whose effects were tested through regression analysis on improvement of IMA.

TABLE 1 MEAN SCORES ACHIEVED ON FIRST AND SECOND EXAMINATION SUBDIVIDED ACCORDING TO THE MEDIAN SEVERITY OF IMA AT FIRST EXAMINATION

	1st exam.	*2nd exam.*	*Difference*	*t*	*df*	*P*
> Initial median severity (n = 13)	45.0	58.8	13.8	5.49	12	< 0.001
⩽ Initial median severity (n = 13)	22.3	40.9	18.6	6.05	12	< 0.001
Total	33.7	49.9	16.2	8.09	25	< 0.001

The correlations between improvement of IMA and improvement in the Token Test, Raven's CPM and oral apraxia were studied by Spearman's Rho. Only subjects with poor performances in both tests could be used to study the correlation of recovery for each pair of variables. Rho values were 0.23 for the PM for 22 subjects ($P = 0.15$, n.s.), 0.32 for the Token Test for 26 subjects ($P = 0.06$) and 0.56 for oral apraxia for 20 subjects ($P = 0.008$). Only the last value can be considered significant.

Eleven of the 13 subjects who were still apraxic at the second examination were examined a third time in order to see whether they continued to improve. One of these patients had had a second stroke and another could not be reexamined. Table 2 shows the scores in the third examination, which in some cases was administered a long time after the second. The mean improvement (9.2) was lower than that which had occurred between the first and second examinations (12.2), but only 5 patients were still apraxic.

TABLE 2. EVOLUTION OF IMA IN 26 ACUTE STROKE PATIENTS

Case	*IMA 1*	*Months*	*IMA 2*	*Months*	*IMA 3**	*Sex*	*Age (yrs)*	*Education (yrs)*
1	43	6.5	69	—	—	M	61	4
2	37	5	60	—	—	M	57	8
3	43	6	69	—	—	M	56	8
4	40	18	63	—	—	M	36	5
5	45	6	60	—	—	M	55	5
6	52	6	67	—	—	M	54	7
7	47	8.5	51	9.5	54	F	71	6
8	50	6	58	—	—	M	69	13
9	40	6	46	13	57	F	49	8
10	46	6	42	6	59	M	32	5
11	43	23.5	57	—	—	M	77	13
12	45	7	58	—	—	M	50	2
13	51	10	65	—	—	F	27	8
14	27	7	62	—	—	F	55	8
15	13	8	49	58	62	F	64	10
16	28	7	46	6.5	46	M	55	5
17	15	8	35	Pt not examined		M	63	3
18	13	5	40	2nd stroke		F	82	8
19	29	7	61	—	—	M	55	10
20	35	7	57	—	—	F	49	8
21	3	9	15	12.5	13	M	61	5
22	18	7	25	14.5	46	M	66	5
23	33	7	45	3	63	M	51	8
24	12	14.5	16	45.5	16	M	60	3
25	30	6	40	7.5	48	M	58	7
26	34	6.5	41	3.5	60	M	62	8

* Third examination score for patients still apraxic at second examination.

Fig. 1 shows the CT scan findings for the 26 patients of our sample. For Cases 13 and 19 the examination did not give useful information as to the site of the lesion, since the scan in Case 13 was marred by artefacts and the hypodensity due to the lesion in Case 19 could not be distinguished from associated oedema. Patients were divided into four groups according to their first examination scores (above or below the median value, i.e., 35), and according to their improvement (above or below the median value, i.e., 14). Within groups 1 and 2, which start from moderate degrees of apraxia, improvement for Cases 5, 6, 11, 12 and 13 were very close to the median value, and it is more informative to focus on Cases 1–4, 7–9 and 10. It appears that the posterior temporal area and the occipitoparietal junction for group 1 cases were well spared, whereas the lesions in group 2 affected these areas to a considerably

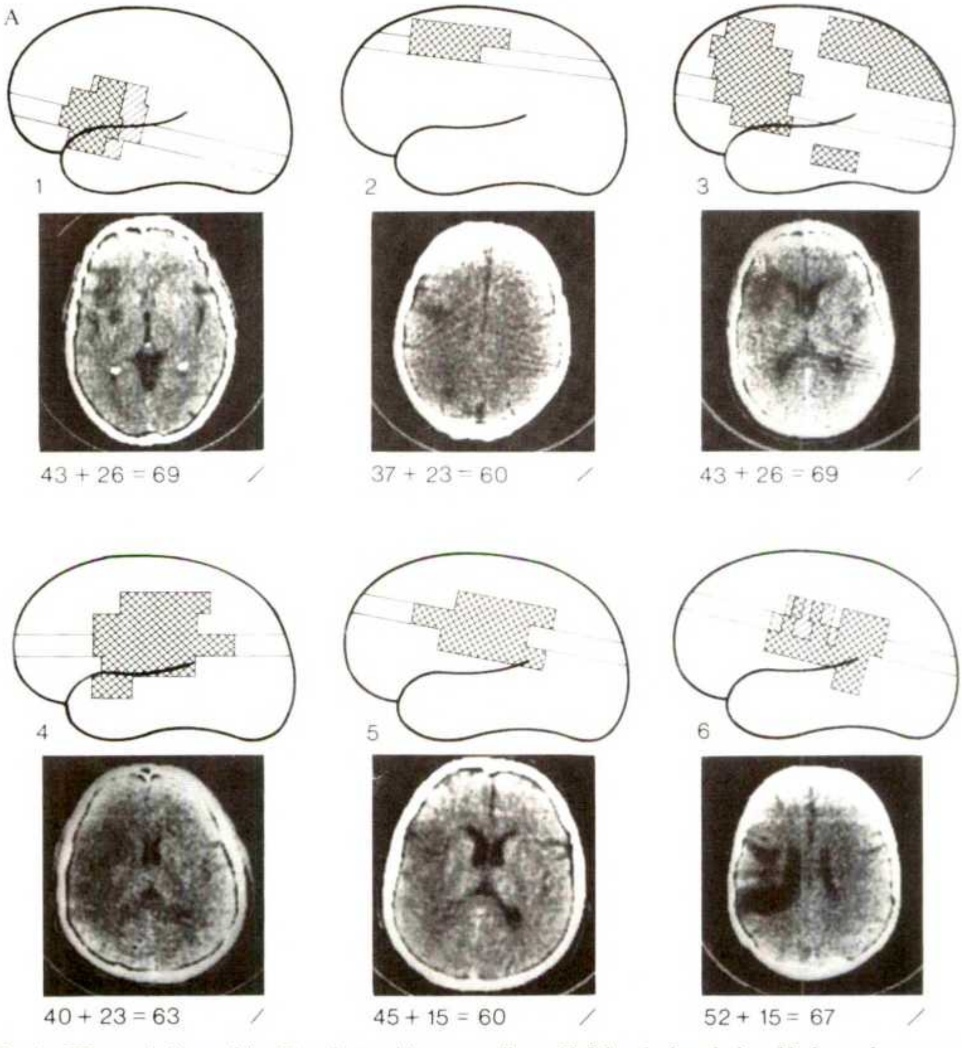
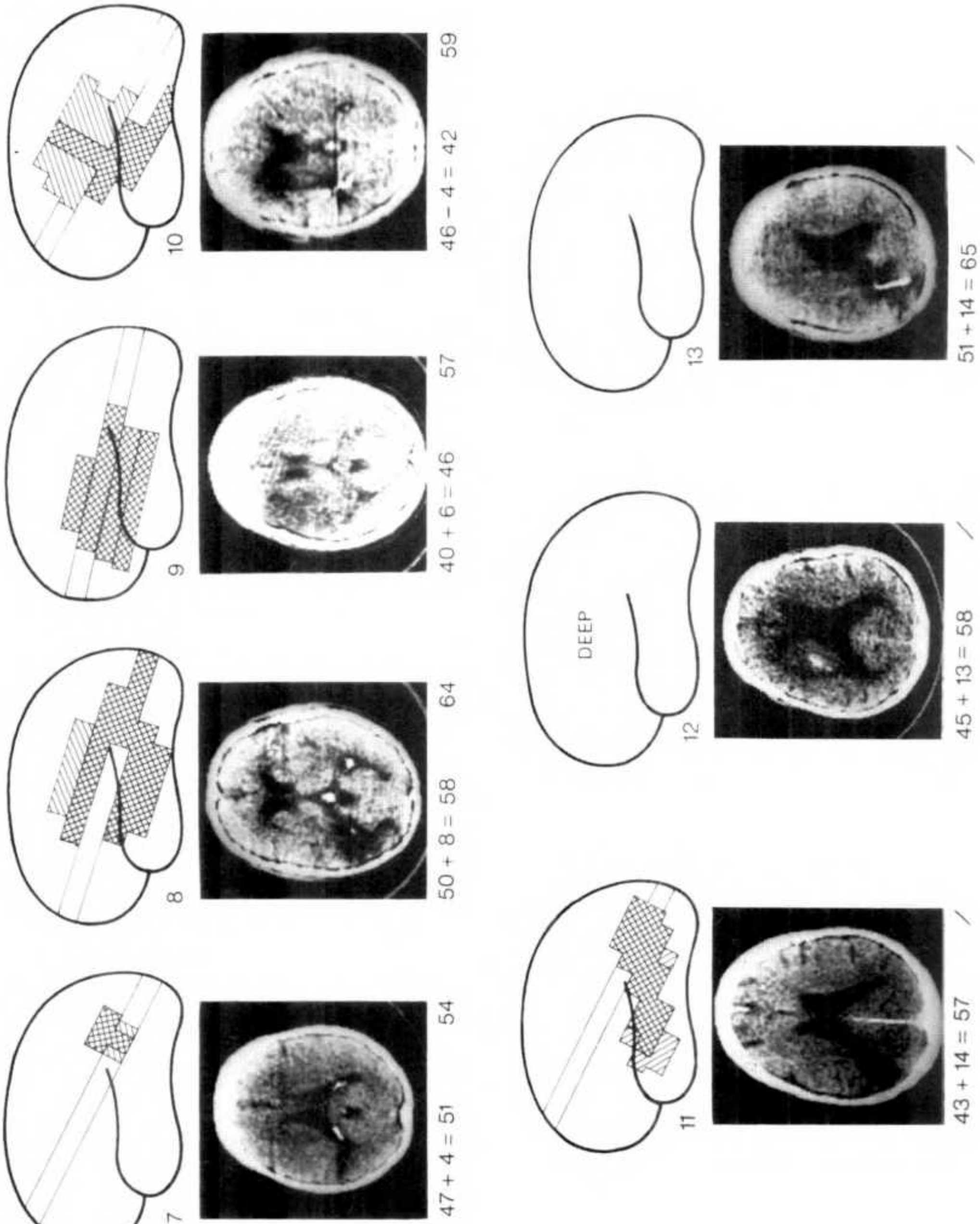
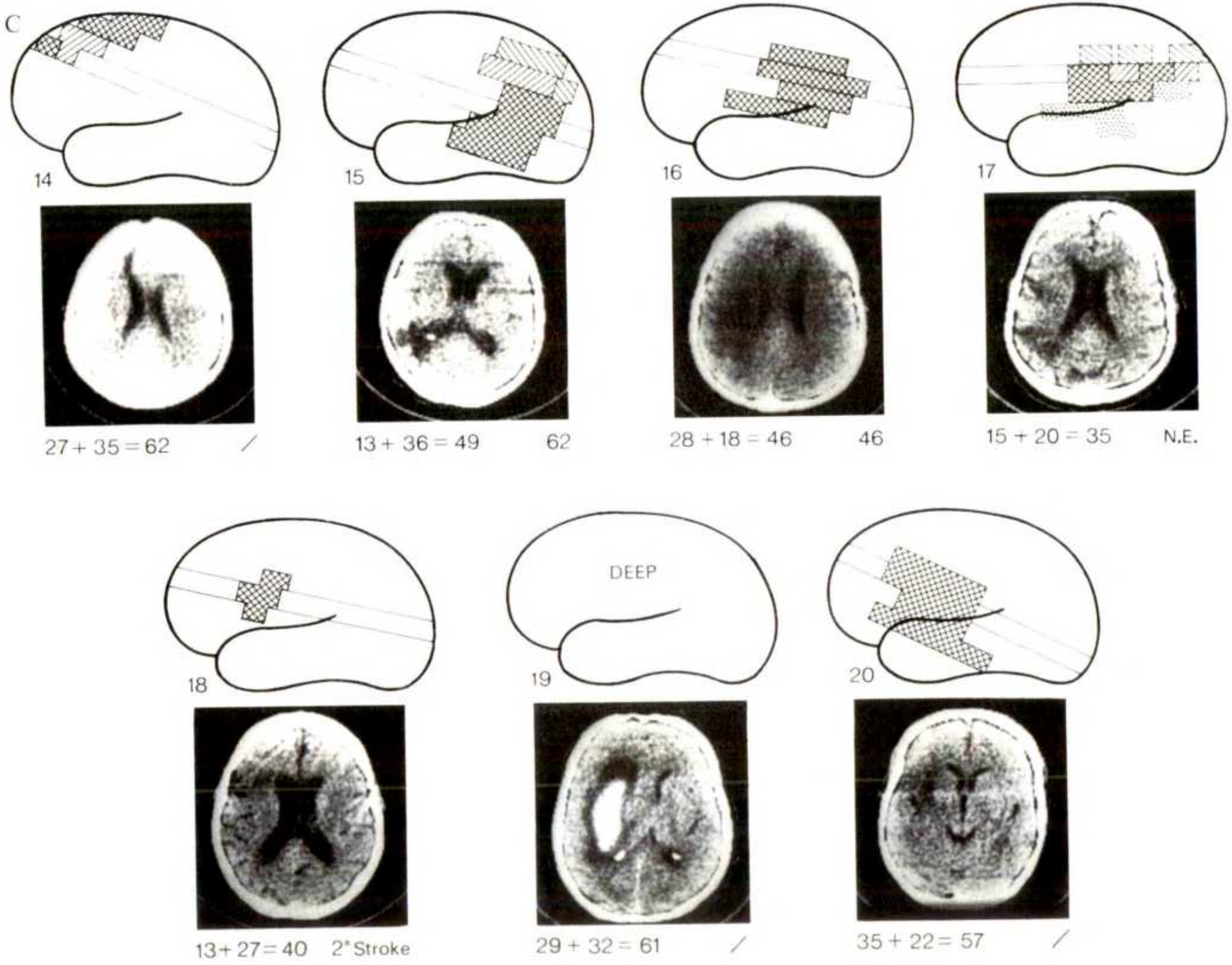


FIG. 1. CT scan findings of the 26 patients with acute unilateral left hemisphere lesion. Under each map are the scores at the first and second examinations; when the latter still indicate apraxic behaviour, a third examination score is shown in the right corner (*see* text and Table 2 for further details). The CT scans correspond to the slice indicated on each lateral diagram. Diagonal lines sloping downwards right to left = deep lesion; left to right = superficial lesion. Dotted area (Case 17) = oedema. All lesions were ischaemic except for those in Cases 10, 12–15 and 19 which were haemorrhagic. A, patient with initial IMA score > 35 and improvement > 14. B–D on following pages. B, patient with initial IMA score > 35 and improvement ⩽ 14; C, patient with initial IMA score ⩽ 35 and improvement > 14; D, patient with initial IMA score ⩽ 35 and improvement ⩽ 14.

greater extent. Incidentally, it should be noted that Case 4, whose lesion touched the temporo-parieto-occipital junction, did improve, but the interval between the first and second examinations was longer than that for the other cases so far considered.

In group 3, Cases 15, 16 and 17 had improved by the second assessment notwithstanding posterior temporal and/or parieto-occipital damage, but it should be noted


B
7
47 + 4 = 51
54
8
50 + 8 = 58
64
9
40 + 6 = 46
57
10
46 − 4 = 42
59
11
43 + 14 = 57
/
12
DEEP
45 + 13 = 58
/
13
51 + 14 = 65
/


C
14
27 + 35 = 62
/
15
13 + 36 = 49
62
16
28 + 18 = 46
46
17
15 + 20 = 35
N.E.
18
13+ 27= 40
2° Stroke
DEEP
19
29 + 32 = 61
/
20
35 + 22 = 57
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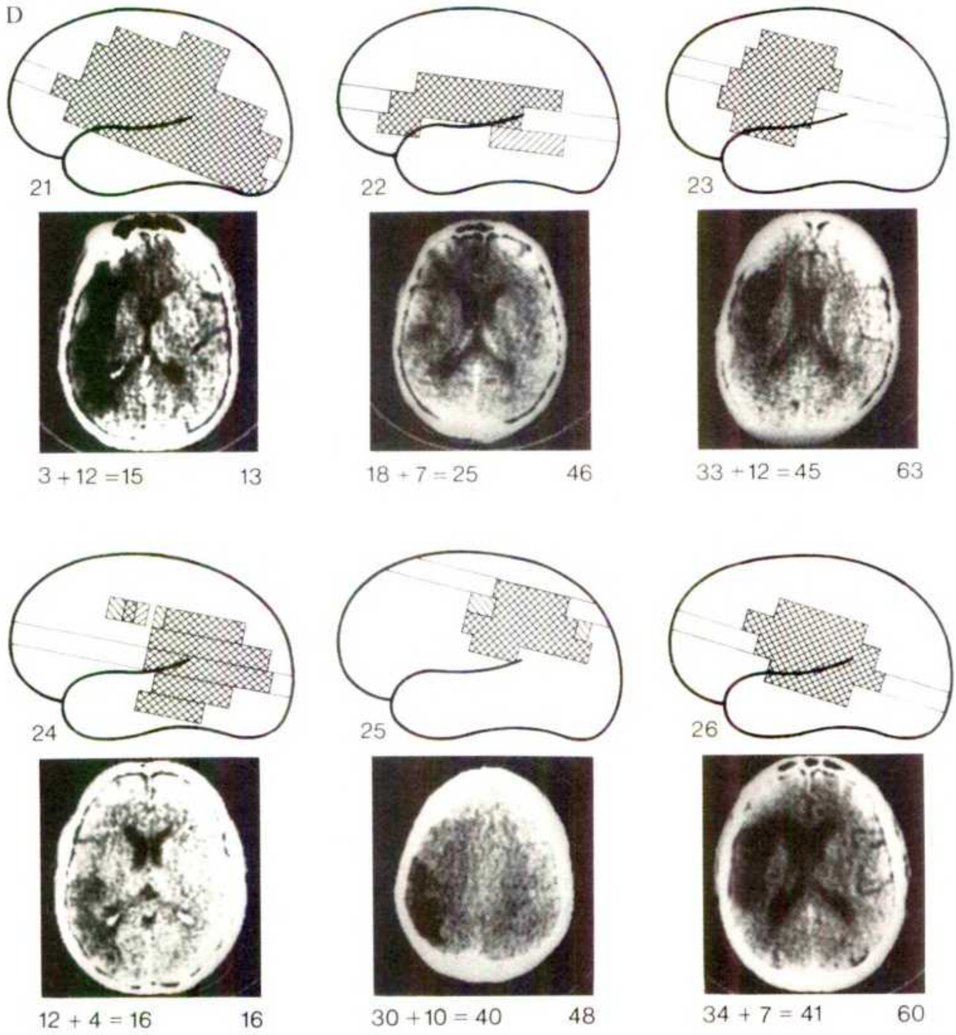

that Case 16 was still apraxic at the third examination. Group 4 patients often had a very large lesion, but it is worth comparing Case 23, who had a mainly anterior/central lesion, with Cases 24 and 25, whose lesions encroached on the brain areas that were mainly damaged in group 2 cases. Although Case 23 was still apraxic at the second examination, three months later, at the third examination, his score was 63 (i.e., definitely normal). On the contrary, Cases 24 and 25 were still apraxic even at the third examination, respectively 45.5 and 7.5 months after the second.

Subjects with Bilateral Lesions

We investigated whether improvement from IMA was the same for this specific sample as that for matched unilateral left hemisphere-damaged patients. Con-

TABLE 3 MEAN SCORES ACHIEVED ON FIRST AND SECOND EXAMINATION OF IMA BY 6 PATIENTS WITH BILATERAL LESIONS (LEFT HAND COLUMNS) AND 13 MATCHED LEFT HEMISPHERE CONTROLS (RIGHT HAND COLUMNS)

	Bilateral patients					*Unilateral matched controls*					
Case	*t.p.o*	*1st–2nd exam.*	*IMA 1*	*IMA 2*	*d*	*t.p.o*	*1st–2nd exam*	*IMA 1*	*IMA 2*	*d*	$\bar{d}$
1	0.5	6.5	17	36	19	1	8	15	35	20	13.5
						1	7	18	25	7	
2	1.5	6.0	46	54	8	2	7.5	48	62	14	6.6
						2	6	46	44	−2	
						2.5	6.5	46	42	−4	
						1	7	48	58	10	
						1	6	45	60	15	
3	6	6.0	46	45	−1	7	6	47	43	−4	−4
4	0.5	6.5	41	58	17	0.5	6	40	46	6	19.3
						0.5	6.5	43	69	26	
						0.5	6	43	69	26	
5	1.5	11	41	47	6	2	11	39	50	11	11
6	0.5	7.0	3	14	11	1	8	3	15	12	12
	Mean				10.0						9.7

t.p.o = time postonset (months), d = difference between 1st and 2nd examination, $\bar{d}$ = mean difference between 1st and 2nd examinations of the controls for each bilateral patient

straints for case-matching were initial IMA severity (±2), length of illness (±15 days for the first month; ±1 month for longer intervals) and interval between first and second examination (±1.5 month). No unilateral matchable subject could be found for 2 patients. The improvement in the remaining 6 bilaterally-damaged apraxic patients who were reexamined was compared with that of 13 unilaterally-damaged apraxic patients and the means were almost identical: 10±7.4 versus 9.74±7.9 (Table 3). Fig. 2 reconstructs the lesions in the bilateral patients.

DISCUSSION

Factors Related to Recovery from IMA: Neural Aspects

Analysis of the outcome for the 26 acute patients shows that a considerable proportion of our patients recovered from IMA, that improvement often requires a long period of time, and that this is apparently not related to age, education, sex, type of aphasia, initial severity or size of lesion. Of our 26 acute patients, 13 were still apraxic at the second examination, but only 5 of 24 were still apraxic at the third assessment.

Analysis of CT scan maps suggests that sparing of posterior temporoparietal and occipital regions is important for recovery of this function, but that some cases can apparently draw upon different resources for substantial improvement. It is possible that the regions able to take over are located within the left hemisphere itself, but they may also be right hemisphere structures.

The apparent discrepancy between the fact that the type of aphasia (fluent vs nonfluent) has no effect on recovery whereas the location of the lesion (anterior vs

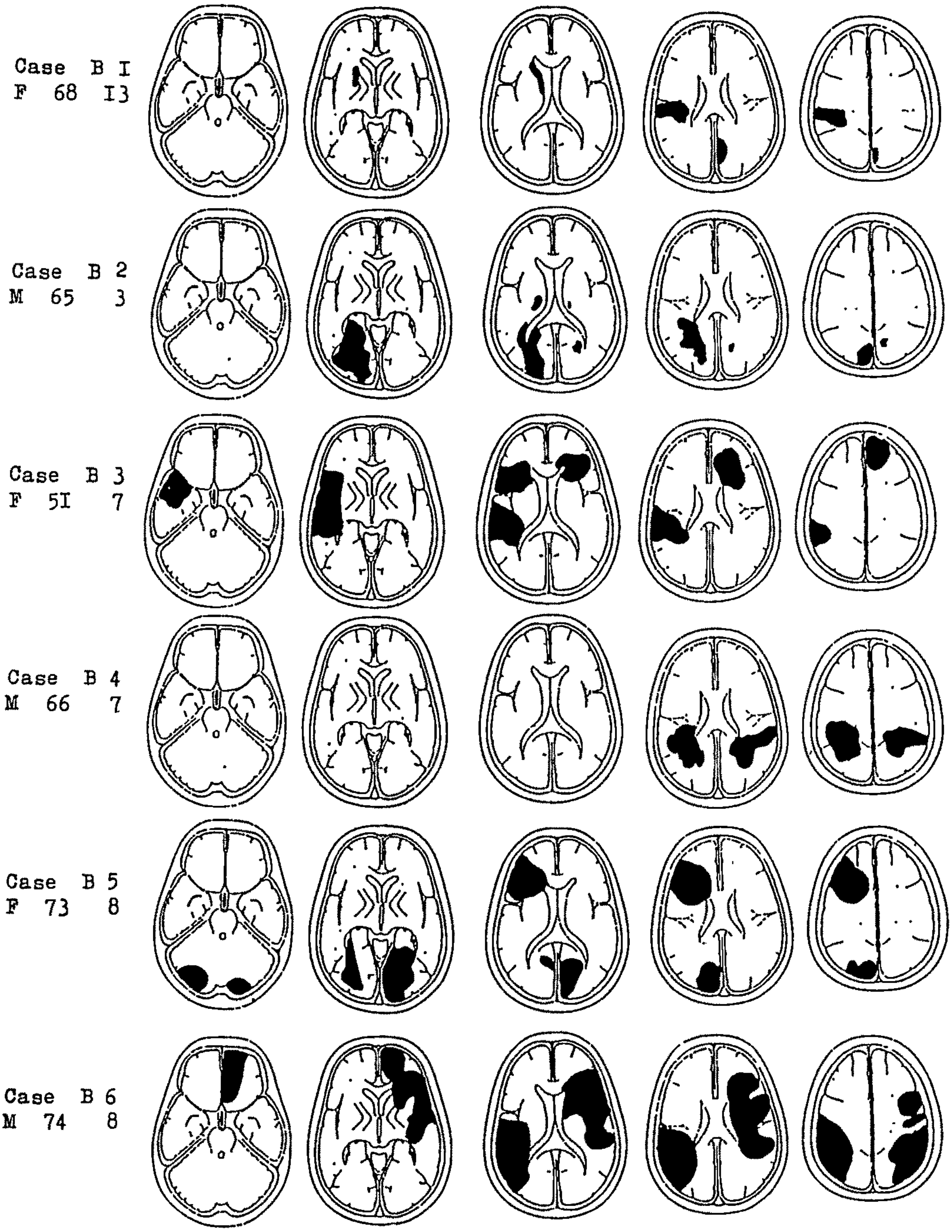

FIG. 2 Site of lesion in the 6 patients with bilateral ischaemic lesions.

posterior) seems to be important can probably be explained on the basis of a posterior lesion being insufficient to prevent recovery, and the fact that there are a certain number, albeit few, of nonfluent patients with posterior lesions and of fluent patients with anterior lesions (Basso *et al.*, 1985). Posterior left hemisphere areas, on the other hand, are often pointed to as crucial for IMA. For example, Faglioni and Basso (1985) indicated that lesions in the parietal lobe cause IMA much more frequently and probably more severely than frontal lesions, even though the latter are also associated with many cases of IMA.

The general conclusion to be drawn from our cases is that there is no one brain area a lesion of which is sufficient to prevent recovery, and even patients with posterior temporal and parieto-occipital lesions may eventually recover from apraxia, even starting from a very low baseline (e.g., Case 15). Nevertheless the lower posterior brain regions appear to affect recovery for the following reasons. Patients who were still apraxic at the third examination always had damage in these areas, whereas they did not always have frontal/central lesions (e.g., Case 25; note also Case 7, who still had a low/borderline score notwithstanding a very small lesion confined to posterior areas). Moreover, integrity of the lower posterior convexity is *sufficient*, although not *necessary*, for good improvement (as already discussed, Case 23 is not a true exception to this statement). In other words, we suggest that the patients with poor prognoses are those with damage to the posterior temporal area and the parieto-occipital junction, although some of them may recover notwithstanding these lesions.

The lack of any significant effect of lesion size on the chance of recovery may have resulted from the fact that we assessed the evolution from the first to the second examination, regardless of the baseline from which recovery was starting, and recovery from a very low score may be possible to a certain extent even if the patient does not eventually recover normal function. Some patients, however (e.g., Cases 3, 4, 26), even with large lesions, may eventually return to a normal level.

Factors Related to IMA Recovery: Neuropsychological Aspects

Our data allowed us to study the relationship between the evolution of IMA and that of other neuropsychological skills that are often affected by left hemisphere damage. Rank correlations between recovery from IMA and recovery of other abilities have much higher values for oral apraxia than for the Token Test or Raven's CPM. This outcome suggests that recovery from IMA and from oral apraxia depends to a considerable extent on the reactivation of common resources, which are greater than the part shared by IMA with the neural substrate for the Token Test or Raven's CPM. Independence of oral apraxia and IMA is not unanimously accepted. Lehmkuhl *et al.* (1983) could not demonstrate with a cluster analysis different apraxic syndromes when they considered differential effects on parts of the body, and Poeck (1985) explicitly stated that 'the traditional distinction between oral and limb apraxia appears quite artificial' (p. 103). If this is so, the strict relationship between oral apraxia and recovery from IMA that we have found would be of no great interest. There are, however, patients with either oral apraxia or IMA alone, and this cautions us against considering the two to be one and the same thing. Tognola and Vignolo (1980) have correlated the site of the left hemisphere lesion, determined by CT scan, with oral apraxia. Performance was less dependent on the integrity of the inferior parietal region than on that of the frontal and central opercular regions and the anterior insula. The patients of Kolb and Milner (1981) with parietal lobe lesions were not impaired in the imitation of facial movement sequences, but compared with frontal, temporal or occipital patients, they were the most impaired group in copying arm movements.

Considering the outcome after six months in the 20 patients of our series who had both oral and ideomotor apraxia at the first examination, 6 still showed oral but not ideomotor apraxia, and one was the reverse on second examination. In any case, if oral and ideomotor apraxia are distinct defects, our data would indicate that they use neurological resources to a large extent held in common.

In summary, there are indications that (1) left parietal regions are more specific than frontal areas for IMA, whereas the opposite is true for oral apraxia; (2) IMA has stricter relationships to oral apraxia than to either the Token Test or Raven's CPM; and (3) IMA is more likely to be found in early left hemisphere frontal lesions than in old frontal lesions. On this basis it is tempting to hypothesize that the overlap between the oral and ideomotor praxis systems is possibly in the anterior left hemisphere areas, more important for oral praxis. These areas would have a higher probability of being replaced by others in the case of the ideomotor praxis system rather than the oral praxis system.

Bilateral Lesions

While the leading role of the left hemisphere in movement planning and learning is not controversial, there are strands of evidence in favour of the right hemisphere having not only an executive function. 'Let us remember once and for all that the right hemisphere also takes part in eupraxis, especially in relation to the left half of the body' (Liepmann, 1920, p. 531). In the first place, clinical evidence suggests that the most severe and long-lasting apraxias tend to be seen in patients with bilateral lesions. Hécaen and Rondot (1985) considered that right hemisphere damage is suggested in some cases of unilateral left apraxia. Finally, a number of patients with right hemisphere damage perform worse than controls when apraxia is assessed with a quantitative procedure (De Renzi *et al.*, 1980).

In our sample, contrary to what would be expected, the right hemisphere did not seem to play any definite role in recovery from apraxia. Bilaterally-damaged patients improved as much as their controls with left hemisphere damage. One possible criticism of the analysis of recovery in bilateral patients is the fact that the matching of the patients could not take into account the lesion sites, which appeared to be important in the analysis of unilaterally-damaged subjects. However, even should a difference be found after better matching, it appears on the whole that the detrimental role of a second contralateral lesion is not as considerable as appears from isolated case reports.

At this stage, because of the small number of cases, it is not possible to assess whether or not bilateral lesions of the temporo-parieto-occipital junction are sufficient to prevent recovery, as would be expected if cases improving despite posterior left hemisphere damage are helped by contralateral homologous regions. In Case 4B lesions were posterior and symmetrically placed but they spared the cortical mantle and this fact prevents us from drawing any definite conclusions.

As a final remark, we wish to stress that the time after onset is a very crucial factor in modelling the pattern of anatomical-functional correlation. Early examinations in fact reveal that even severe apraxia is associated with small anterior lesions (*see*, for example, Cases 2 and 18). Our data on the relationship between the site of the lesion and recovery appear to give more specific information and this possibly will prove to be applicable to the study of other neuropsychological functions.

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BRADYPHRENIA IN PARKINSON'S DISEASE AND PSYCHOMOTOR RETARDATION IN DEPRESSIVE ILLNESS

AN EXPERIMENTAL STUDY

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SUMMARY

Thirty newly diagnosed patients with Parkinson's disease and 30 patients with primary depressive illness showed slowing of response on a computerized digit symbol substitution test when compared with 30 matched normal control subjects. Significant slowing was related, in the parkinsonian patients, to structural brain disorder and affective impairment and, in the depressed patients, to motor impairment. A second computerized test, cognitively simpler but requiring the same motor response, was also administered to each subject. Both cognitive and motor slowing seemed to contribute to slowing of response in the digit symbol test in both parkinsonian and depressed patients. The tests were repeated after about six months in 12 subjects from each group. The parkinsonian patients, on dopaminergic treatment, showed neither significant change in motor or affective impairment, nor improvement in response time for the digit symbol test, but change in response time was related to change in depression rating. The depressed patients, on conventional treatment, showed significant improvement in both affective and motor impairment and improvement in response time for the digit symbol test, due to improvement in cognitive slowing. It is proposed that bradyphrenia in Parkinson's disease and psychomotor retardation in depressive illness are closely related, and that impairment of dopaminergic systems may be involved in both.

INTRODUCTION

Bradyphrenia, or slowing of cognitive processing associated with impairment of concentration and apathy, was first described as a psychiatric syndrome in association with parkinsonism in the wake of the encephalitis lethargica pandemic of the 1920s. Clinical descriptions of this syndrome, and its more recent synonyms psychic akinesia and subcortical dementia, have been consistent over the last sixty years (Rogers, 1986). Opinion has been divided over whether this cognitive slowing is apparent or real, and experimental studies have produced conflicting results. Naville (1922), who introduced the term bradyphrenia, devised a series of tests in

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which the motor element remained the same but the intellectual difficulty varied. These showed slowing of intellectual function in his parkinsonian patients compared with normal subjects, and a relationship between intellectual and motor slowing. Shortly afterwards, however, Worster-Drought and Hardcastle (1924), using the same principle to test 19 postencephalitic patients, found that while 'psychomotor reaction time' was lengthened compared with control subjects, 'cerebration time' was not appreciably affected.

Recently there has been renewed interest in the syndrome of bradyphrenia with attempts to define its neuroanatomical and neurochemical basis (Agid *et al.*, 1984), but the apparent conflict between different experimental results continues. Wilson *et al.* (1980) measured speed and accuracy of short-term memory scanning in 20 parkinsonian patients and 16 normal controls, matched for age and education. Finding that scanning speed of elements held in short-term memory was increased in a subgroup of elderly patients, they suggested that parkinsonian slowing might include a cognitive slowing, or bradyphrenia. Hansch *et al.* (1982) found a significant, age-independent negative correlation between the score of 20 parkinsonian patients on a symbol digit test and the latency of the P300 component of an auditory event-related potential, the patients showing significantly increased P300 latencies compared with normal controls. They suggested that the digit-symbol test score and P300 latency reflected a common disrupted aspect of cognitive function in Parkinson's disease, for which bradyphrenia was an apt description. In contrast, Rafal *et al.* (1984) studied the performance of 10 patients with Parkinson's disease on rate of memory scanning, orientating of attention in the visual fields and the time required to prepare a manual movement, the patients serving as their own controls at different stages of treatment with L-DOPA, including during 'on' and 'off' states. The authors found that overall reaction time increased when patients were in the untreated state, but without a concomitant slowing of purely cognitive components, and cautioned against inferring a slowing of thought processes from increased response latencies.

Historically there has been a changing appreciation of the nature of akinesia, one of the major symptoms of motor impairment in parkinsonism (Ajuriaguerra, 1970*b*). For Naville (1922), bradyphrenia was a psychiatric syndrome although many of the motor features he described would now be classified as akinesia. More recently, the terms bradyphrenia and psychic akinesia have been used interchangeably (Ajuriaguerra, 1970*a*). Different experimental studies of reaction times and motor performance in parkinsonian patients have shown slowing of movement suggesting 'central motor disorder' as well as more peripheral impairment (Brumlik and Boshes, 1966; Angel *et al.*, 1970; Evarts *et al.*, 1981). This 'central motor disorder' might contribute to what others have described as bradyphrenia, and differing perceptions of 'central slowing' as a motor or a mental phenomenon might explain some of the conflict in findings between different studies of cognitive slowing in parkinsonian patients. Another factor could be the selection of patients for study, especially with regard to associated affective disorder. Depression is a feature of a significant number of patients with Parkinson's disease, and has its own classically described slowing of movement and cognitive function. The cerebral localization offered for akinesia, bradyphrenia and the psychomotor slowing in psychiatric disorders has been strikingly similar (Ajuriaguerra, 1971*b*; Hicks and Birren, 1970; Agid *et al.*, 1984) and it may be that there is more significance in the similarity between these different phenomena than traditional divisions between neurology and psychiatry would allow.

The aim of the present study was to establish whether slowing of cognitive processing could be demonstrated in unselected, newly diagnosed patients with Parkinson's disease and, if so, its association with motor impairment, affective disorder and response to L-DOPA therapy. In an attempt to explore the relationship between Parkinson's disease and affective disorder, the same procedure was used in patients with primary affective illness on conventional treatment.

PATIENTS AND METHODS

Thirty consecutively referred newly diagnosed patients with Parkinson's disease, before treatment with L-DOPA, 30 normal controls, aged over 35 years, free of neuropsychiatric illness and 30 consecutively referred patients, aged over 35 years, with primary depressive illness, were examined. The patients with Parkinson's disease all fulfilled the UK Parkinson's Disease Society (PDS) brain bank diagnostic criteria (*see* Appendix). The patients with primary depressive illness were referred either to the psychiatric department of a neurological hospital, or to a district psychiatric hospital. They all fulfilled all six of the Research Diagnostic Criteria (RDC) for major depressive disorder (Spitzer *et al.*, 1978).

The three groups were similar for age, years of education, and premorbid IQ using the National Adult Reading Test (NART) (Nelson and O'Connell, 1978). None of the patients was clinically demented. Twenty-eight parkinsonian patients and 18 depressed patients had a full psychological assessment. The median full scale WAIS IQ in the parkinsonian patients was 105 (range 66–126), with a median verbal IQ of 105.5 (range 86–129) and median performance IQ of 106.5 (range 75–120), and in the depressed patients 107 (range 90–134), with a median verbal IQ of 108 (range 93–136) and median performance IQ of 101 (range 86–130).

Twenty-seven of the parkinsonian patients and 21 of the depressed patients had CT scans; 9 of the parkinsonian patients' scans were reported as showing structural brain disorder: varying degrees of cerebral atrophy in 8, and focal lesions in 3 (thalamic lacunar infarct, frontal lobe infarct, and white matter ischaemic changes with basal ganglia and capsular infarcts). Two parkinsonian patients' scans were reported to show atrophy and focal lesions and 3 of the depressed patients' scans were reported as showing structural disorder, atrophy in 2 and a focal lesion in 1 (midbrain infarct). All remaining scans were reported as normal.

The parkinsonian patients (PP) were tested before starting dopaminergic agonists, but 12 of them, 25 of the depression patients (DP) and 3 of the normal controls (NC) were taking neurotropic medication. This comprised benzodiazepines (5 PP, 18 DP and 2 NC), antidepressants (3 PP, 14 DP and 1 NC), anticholinergics (4 PP), anticonvulsants (3 DP) and neuroleptics (2 DP).

All subjects were rated with the Webster rating scale for Parkinson's disease (Webster, 1968), to assess motor impairment, and with the 17-item Hamilton rating scale for primary depressive illness (Hamilton, 1967) to assess affective impairment. The number of positive items on the symptom checklist (maximum 8) of the Research Diagnostic Criteria (RDC) for major affective disorder (Spitzer *et al.*, 1978) was also noted in each subject.

After completing the clinical ratings, two tests, varying in cognitive difficulty but involving the same motor response, were administered to each subject using a microprocessor, 9 × 7 in TV screen and response keyboard with 9 keys numbered 1-9. One was a digit symbol substitution test (DST). The stimuli were 1 of 9 symbols appearing individually in random sequence on the screen. Each symbol was arbitrarily paired with a digit between 1 and 9. A table giving the 9 pairings remained on the screen continuously. The response was the pressing of the appropriate number key. For the simpler task, the stimuli were digits between 1 and 9 which appeared individually in random sequence on the screen. The required response was the pressing of the same number key. The simpler test was performed before the digit symbol test. In both tests there were 60 test trials preceded by practice trials (4 for the simpler test and 10 for the DST). The subjects were asked to use the index finger of their preferred hand for writing, keeping this stationed on a fixed point on the keyboard between responses. An instruction to go as fast as they could appeared on the screen with each trial. Response times were measured to the nearest 0.01 s, and the mean response time for the 60 trials of each test calculated. Wrong responses were recorded but response times recorded only on pressing of the correct key.

The motor responses required in both tests were identical. The difference between the response times for the two tests was the time required to perform the additional component of the digit symbol substitution task. This additional component involved both a cognitive and a visual scanning element. This was called 'matching time'. It was calculated by subtracting the mean response time for the simpler test from the mean response for the digit symbol test. As an additional measure of motor impairment relevant to the movement required in the cognitive tests, a subgroup of subjects (18 of the parkinsonian group, 22 of the depressed group and all 30 normal controls) were asked to press, as quickly as possible, each of the nine buttons on the keyboard, starting from and returning to the same fixed point between presses. This was repeated three times and the total time taken for the 54 journeys recorded. The total time divided by the number of journeys gave an estimate of the mean time required to perform the movement used in the test responses. This was called 'movement time'. This test was performed with the other clinical assessments before the computerized tests. Visual acuity for near vision was measured at the site of testing. The effect of fatigue was assessed by comparing the mean response time for the first 20 and the last 20 of the 60 trials of each of the computerized tests.

The clinical ratings and the two cognitive tests were repeated in exactly the same way on a second occasion in 12 subjects from each group selected on grounds of availability. The median interval between tests for the parkinsonian group was 180 days (range 110-403), for the depressed group 234.5 days (range 17-422) and for the normal controls 235.5 days (range 23-339).

In both patient groups, the proportion of patients with structural disorder reported on CT scan was similar in the subgroups retested to that in the original groups. Of the 11 parkinsonian patients retested who had had a CT scan, 4 had had cerebral atrophy reported. Of the 10 depressed patients retested who had had a CT scan, 1 had had cerebral atrophy and 1 a focal lesion reported.

On retesting, all 12 of the parkinsonian patients were now taking a dopaminergic agonist (10 L-DOPA, 1 bromocriptine, 1 pergolide). The proportion of subjects in the different groups taking neurotropic medication on retesting was otherwise similar to that on first testing: benzodiazepines (1 PP, 6 DP, 1 NC on first testing; 1 PP, 5 DP, 1 NC on retesting), antidepressants (1 PP, 5 DP on first testing and retesting), anticholinergics (2 PP on first testing; 1 PP on retesting), anticonvulsants (1 DP on first testing and retesting) and neuroleptics (1 DP on first testing and 2 DP on retesting).

Statistical Methods

Analysis of variance was used to compare ages in the three groups. Otherwise, because the continuous variables measured were not normally distributed, nonparametric analysis was used. The Kruskal-Wallis one-way analysis of variance was used to compare the results of the three experimental groups. Only when significant group differences were obtained from this analysis were these elaborated using the Mann-Whitney U-test to compare pairs of groups. The Mann-Whitney U-test was also used to compare differences within groups. Further analyses included the Spearman correlation coefficient with two-tailed test of significance, and Wilcoxon matched-pairs test to compare test-retest data. Contingency tables were analysed using the χ^2 statistic. In view of the number of statistical comparisons made, a significance level of $P < 0.01$ was adopted throughout.

RESULTS

There were no statistically significant differences between the three subject groups for age, years of education or premorbid (NART) IQ, or in distribution of sex, handedness or visual acuity (Table 1).

Both the Webster and Hamilton rating scores of the three groups (Table 2), were significantly different ($P < 0.0001$ in either case). There were significant differences in the ratings of both motor and affective impairment between either patient group and the normal controls, and between the two patient groups. Of note is that the affective impairment of the parkinsonian patients and the motor impairment of the depressed patients were significantly different from those of the normal controls.

There were significant differences between the three groups for response time on the digit symbol test ($P < 0.001$), and also for response time time on the simpler test ($P < 0.0001$) and movement time ($P < 0.001$) (Table 3). Response times for both tests and movement time were significantly prolonged in both parkinsonian and depressed patients compared with the normal controls, but the differences between the two patient groups were not significant. Differences in matching time between the three groups did not achieve statistical significance, although matching times were greater in the two patient groups than in the normal controls (Table 3).

The difference in mean response time for the first 20 and last 20 of the 60 trials

TABLE 1. MEAN AND RANGE FOR AGE, MEDIANS AND RANGES FOR YEARS OF EDUCATION AND PREMORBID (NART) IQ, AND DISTRIBUTION OF SEX, HANDEDNESS AND VISUAL ACUITY

	Age (yrs)	*Years of education*	*NART (premorbid) IQ*	*Sex (M.F)*	*Handedness (R.L)*	*Visual acuity (<N6 >N6)*
Controls (n = 30)	60 5 (37–79)	11 (4–19)	115 5 (91–126)	12.18	24:6	24:4
Parkinsonians (n = 30)	58 9 (35–79)	10 5 (8–19)	116 (88–126)	19·11	29·1	20 8
Depression (n = 30)	57.9 (35–78)	10 (7–18)	110 (89–124)	14 16	26 4	20 7

TABLE 2 MEDIANS AND RANGES FOR WEBSTER (MOTOR IMPAIRMENT) AND HAMILTON (DEPRESSION) RATING

	Webster rating	*Hamilton rating*
Controls (n = 30)	0 (0–2)	0 5 (0–10)
Parkinsonians (n = 30)	12 (3–21)	9 (1–24)
Depression (n = 30)	5 (0–13)	21 (12–32)

* $P < 0 001$

TABLE 3 MEDIANS AND RANGES FOR RESPONSE TIME FOR TWO COMPUTERIZED TESTS, MATCHING TIME AND MOVEMENT TIME

<table>
<tr><th></th><th></th><th><i>Response time digit symbol test (s)</i></th><th></th><th></th><th><i>Response time simpler test (s)</i></th><th></th><th><i>Matching time (s)</i></th><th></th><th><i>Movement time (s)</i></th><th></th></tr>
<tr><td>Controls (n = 30)</td><td rowspan="2">*</td><td>1.80 (1.43–2.94)</td><td rowspan="3">*</td><td rowspan="2">**</td><td>0.97 (0.78–1.40)</td><td rowspan="3">**</td><td>0.79 (0.42–1.58)</td><td rowspan="2">*</td><td>0.37 (0.26–0.54)</td><td rowspan="3">**</td></tr>
<tr><td>Parkinsonians (n = 30)</td><td>2.19 (1.45–10.94)</td><td>1.14 (0.87–2.52)</td><td>0.97 (0.52–8.56)</td><td>0.48 (0.29–0.77)</td></tr>
<tr><td>Depression (n = 30)</td><td></td><td>2.12 (1.55–9.80)</td><td></td><td>1.17 (0.81–3.35)</td><td>1.01 (0.61–6.45)</td><td></td><td>0.43 (0.30–1.22)</td></tr>
</table>

* $P < 0.01$, ** $P < 0.001$

TABLE 4. MEDIANS AND RANGES FOR DIFFERENCE BETWEEN INITIAL AND FINAL RESPONSE TIMES (MEAN FOR FIRST 20 TRIALS – MEAN FOR LAST 20 TRIALS) OF TWO COMPUTERIZED TESTS

	Difference for digit symbol test (ms)	*Difference for simpler test (ms)*
Controls (n = 30)	1.10 (−1.18–0.51)	0.11 (−0.09–0.93)
Parkinsonians (n = 30)	0.13 (−1.58–0.74)	0.08 (−0.82–0.84)
Depression (n = 30)	0.18 (−0.48–3.71)	0.10 (−0.99–0.96)

of each of the computerized tests was not significantly different for each of the three groups (Table 4). Fatigue during testing was not sufficient to explain the differences between groups.

There was a significant correlation of DST response time with age in the parkinsonian group (0.57, $P < 0.001$) and the normal controls (0.59, $P < 0.001$, but not in the depressed group. There was a significant correlation of DST response time and visual acuity in the parkinsonian group (0.53, $P < 0.01$), but not in the depressed group or normal controls. There were no significant sex differences for DST response time in any group and no correlation with length of illness in the patient groups. DST response times were not significantly different in those taking and those not taking neurotropic medication in any of the three groups.

There was no significant correlation of DST response time with NART IQ in any group, or with WAIS full scale or verbal IQ in either patient group. There was a significant negative correlation of DST response time with performance IQ (−0.56, $P < 0.01$) in the parkinsonian group but not the depression group. Ten parkinsonian patients and 6 depressed patients had a full scale IQ less than their estimated premorbid IQ by 10 or more points. In both groups, these patients did not have significantly slower DST response times than the patients whose IQ difference was less than 10 points. There were no significant differences in the number of erroneous responses, which would automatically increase response times, between any of the three subject groups in either of the computerized tests.

In the parkinsonian patients, the 9 with structural disorder reported on CT scan had a significantly greater DST response time ($P = 0.001$) than the 18 without. In contrast to the whole parkinsonian group, these 9 patients had a significantly longer matching time ($P < 0.001$) than the normal controls. In the 18 parkinsonian patients without structural brain disorder, DST response time was no longer significantly different from that in the normal control group.

In the parkinsonian patients, response time for the DST and simpler test, matching time and movement time were all significantly associated with Webster rating but only DST response time and matching time were significantly associated with Hamilton rating (Table 5). In the depressed patients, response time for the DST and simpler test were significantly associated with Webster rating. Of the 30 parkinsonian patients, 15 had 5–8 positive items on the RDC symptom checklist for major depressive disorder, and 15 had 1–4 items. In contrast to the whole parkinsonian group, matching time was significantly longer than in the normal control group ($P < 0.01$) in those with 5–8 positive items, and DST response time not significantly different from that in the normal controls in those with 1–4 items. Of the 30 depressed patients, 16 had a score of 6–13 on the Webster rating scale for motor impairment, and 14 had a score of 0–5. In contrast to the whole depressed group, matching time was significantly longer than in the normal control group ($P < 0.01$) in those with a score of 6–13, and DST response time was not significantly different from that in the normal controls in those with a score of 0–5.

TABLE 5 SPEARMAN CORRELATION COEFFICIENTS BETWEEN WEBSTER AND HAMILTON RATINGS AND RESPONSE TIMES FOR DIGIT SYMBOL TEST AND SIMPLER TEST, MATCHING TIME AND MOTOR TIME

	Response time digit symbol test	*Response time simpler test*	*Matching time*	*Movement time*
Parkinson's disease	(n = 30)	(n = 30)	(n = 30)	(n = 18)
Webster rating	0.55*	0.51*	0.52*	0.64*
Hamilton rating	0.48*	0.37	0.50*	0.51
Primary depression	(n = 30)	(n = 30)	(n = 30)	(n = 22)
Webster rating	0.55*	0.60**	0.35	0.48
Hamilton rating	0.26	0.32	0.16	0.07

* $P < 0.01$, ** $P < 0.001$

Twelve subjects were retested in each group. The differences in interval between tests for the three groups were not statistically significant. On retesting, there was significant improvement in Webster and Hamilton rating in the depression group but not the parkinsonian group (Table 6). Total DST response time and matching time, but not response time for the simpler test or movement time, improved significantly in the depression group. None of these measures improved significantly in the parkinsonian group. Nevertheless, change in DST response

TABLE 6 MEDIANS FOR WEBSTER AND HAMILTON RATINGS, RESPONSE TIMES FOR TWO COMPUTERIZED TESTS, MATCHING AND MOVEMENT TIME, ON FIRST AND SECOND TESTING

	Webster rating		*Hamilton rating*		*Response time digit symbol test (s)*		*Response time simpler test (s)*		*Matching time*			*Movement time (s)*	
	Test 1	*Test 2*	*Test 1*	*Test 2*	*Test 1*	*Test 2*	*Test 1*	*Test 2*	*Test 1*	*Test 2*		*Test 1*	*Test 2*
Controls (n = 12)	0	0	0	0	1.59	1.60	0 89	0 91	0 73	0 72		0.37	0 33
Parkinsonians (n = 12)	14	11	9	8	2 29	2.05	1 30	1 13	1.02	0 80	(n = 7)	0.51	0.50
Depression (n = 12)	6	1 5*	20.5	15*	2.45	2.17*	1 17	1 09	1.10	0 83*	(n = 10)	0.42	0 43

* $P < 0\ 01$

TABLE 7. SPEARMAN CORRELATION COEFFICIENTS BETWEEN CHANGES IN WEBSTER AND HAMILTON RATINGS AND CHANGES IN RESPONSE TIMES FOR TWO COMPUTERIZED TESTS, MATCHING TIME AND MOVEMENT TIME

	Change in response time digit symbol test	*Change in response time simpler test*	*Change in matching time*	*Change in movement time*
Parkinson's disease	(n = 12)	(n = 12)	(n = 12)	(n = 7)
Change in Webster	0.19	0.57	−0 05	0.47
Hamilton rating	0.75*	0.41	0.45	0.72
Primary depression	(n = 12)	(n = 12)	(n = 12)	(n = 10)
Webster rating	0.33	0.40	0.20	−0 28
Hamilton rating	0.69	0.55	0.56	−0.03

* $P < 0.01$

time in the parkinsonian group correlated significantly with change in Hamilton rating (Table 7).

DISCUSSION

The psychomotor measure used in this study, a digit symbol substitution test, was already well established before its incorporation as a subtest of the now most widely used cognitive test battery, the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1958). It is highly sensitive to brain dysfunction without having particular localizing value. In older people, and patients with Parkinson's disease, it shows the most marked decline in performance of any of the subtests of the WAIS (Doppelt and Wallace, 1955; Asso, 1969; Gil and Lefevre, 1979). Pirozzolo *et al.* (1982) examined the performance of 60 patients with idiopathic Parkinson's disease and matched controls on 23 neuropsychological test variables. The parkinsonian patients' performance showed a continuous distribution of cognitive deficit compared with their matched controls, being significantly poorer on 18 of the variables. Stepwise discriminant analysis of the test data, however, showed that a digit symbol test alone appropriately classified 72% of the patients and 87% of normal controls and was as equally effective as individual pathognomonic motor signs in differentiating the two groups. Its dependence on motor control has caused other investigators to omit it from cognitive testing of parkinsonian patients (Fisher and Findley, 1981), but the study (Hansch *et al.*, 1982) showing a correlation between the score on a symbol-digit test and an objective measure of cognitive function, confirmed that slowing of cognitive as well as of motor function contributes to slowing of performance on this test, as had already been suggested (Wechsler, 1958). In untreated patients with depressive illness, performance on a digit symbol test is also significantly impaired compared with normal controls matched for age and education (Friedman, 1964; Weckowicz *et al.*, 1972).

In the present study, an attempt was made to separate the motor and cognitive components of a digit symbol test by using a computerized version of the test together with a second computerized test requiring the same motor response but of lesser cognitive difficulty. Where one test involved both digits and symbols, the other involved only digits. Response times in both tests were reliable measures. Speed of response was constant throughout the 60 trials of each test, and normal subjects showed little change in response times when the same tests were repeated up to 8 months later. The difference in response times for these two tests was taken to represent the time required to perform the extra matching component of the more difficult test (matching time). This cannot be regarded as a pure measure of speed of cognitive processing as it involves a significant visual scanning component. Akinesia of the oculomotor system has been demonstrated in parkinsonian patients (DeJong *et al.*, 1973; White *et al.*, 1983*a*, *b*) and would impair the visual scanning necessary in the digit symbol test. No patient in this study had obvious disorder of eye movements, but no attempt was made to assess akinesia of eye movements separate from general motor impairment, so that the specific contribution of impairment of visual scanning to any increase of matching time could not be assessed. However, matching time can be taken to represent the 'most cognitive' of the components of the total response time for the digit symbol test used in this study, and thus to be a measure of 'bradyphrenia'. The time taken to perform the movement required in the test responses, the 'most motor' of its components, was separately assessed (movement time).

Thirty newly diagnosed patients with Parkinson's disease showed a significant degree of slowing of response time in the computerized digit symbol test, compared with 30 normal controls, but not compared with 30 patients with primary depressive illness. Slowing of response was present from the outset of the 60 trials of the test in both groups of patients. The three groups of subjects were matched for age, premorbid IQ and visual acuity, so that these factors, while contributing to slowing of response in individual subjects, could not explain the difference in response times between the groups. Neurotropic medication had no significant effect on slowing of response and, on retesting, improvement occurred despite or because of these medications, consistent with reported effects of antidepressant medication on cognitive function (Thompson and Trimble, 1982). In both groups of patients, slowing of response was found with no significant impairment of general intellectual function, consistent with reports of subtle cognitive changes in early untreated Parkinson's disease (Lees and Smith, 1983) and cognitive functioning in depressive illness (McAllister, 1981). There was an association of response time for the digit symbol test with structural disorder demonstrated on CT scan, motor impairment and depression rating in the parkinsonian patients, and with motor impairment in the depressed patients.

Considering the components of the total response time for the digit symbol test, response time for the simpler test and movement time were significantly slower in both patient groups compared with normal controls. Response time for the simpler test was associated with clinically rated motor impairment in both patient groups, and movement time was associated with motor impairment in the parkinsonian patients. This confirms the contribution of motor impairment to performance of the digit symbol test, and the presence of motor impairment in the depressed patients. Matching time, however, was not significantly prolonged in either patient group, compared with the normal control group. One might therefore conclude that there is no specific slowing of the cognitive component of the digit symbol test in either parkinsonian or depressed patients. However, further findings modify this conclusion. Matching time in the parkinsonian patients was associated with both clinically rated motor impairment and depression rating. The 9 parkinsonian patients with structural disorder on CT scan did show a significant prolongation of the matching time component of response time for the digit symbol test, compared with the normal controls, whereas the 18 without structural disorder did not even show significant slowing of response time for the digit symbol test. Similarly, the 15 parkinsonian patients with 5–8 positive items on the RDC checklist for major depressive disorder had a significant prolongation of matching time, while the 15 with only 1-4 positive items had no significant slowing of response time for the digit symbol test. The 16 depressed patients with a Webster rating score for motor impairment of 6-13 had a significant prolongation of matching time, while the 14 with a score of 0-5 had no significant slowing of response time for the digit symbol test. Thus slowing of response in a cognitive test is only a significant feature in a proportion of patients with parkinsonism, and a proportion of patients with depressive illness. When slowing is present, slowing of cognitive processing, or bradyphrenia, seems to contribute to it. This slowing of cognitive processing is associated with the presence of structural brain disorder and affective disorder in parkinsonian patients, and motor impairment in depressed patients.

After 3 to 12 months, 12 of the parkinsonian patients, who had all been treated with a dopaminergic agonist, did not show significant change in motor impairment or depression rating. These patients did not show significant change in response time for the digit symbol test. This is in contrast to other studies which have shown a significant improvement in performance on a digit symbol test following treatment with L-DOPA (Beardsley and Puletti, 1971; Portin and Rinne, 1980). They did, however, show a significant association between change in response time for the digit symbol test and change in depression rating. Twelve of the depressed patients, who had received conventional treatment over a comparable length of time, showed significant improvement in both depression rating and motor impairment. These patients did show a significant improvement in response time for the digit symbol test. This was not due to a practice effect, as 12 of the normal controls showed no change in any of the experimental measures when retested after a comparable period. Furthermore, the depressed patients showed a significant improvement in matching time, but not in response time for the simpler cognitive test or movement time. The results of retesting confirm the association, in both Parkinson's disease and depressive illness, between the measure of bradyphrenia use in this study, and affective disturbance.

The findings of this study support the concept of an overlap between Parkinson's disease and depressive illness. Different studies have consistently shown that between 40 and 50 % of patients with Parkinson's disease develop symptoms sufficient for a diagnosis of depression at some point during the course of their illness (Mayeux *et al.* 1984). In this study, 30 newly diagnosed patients with Parkinson's disease had a significantly higher mean Hamilton depression rating than a group of matched normal controls, their Hamilton scores overlapping with both the normal controls and patients with primary depressive illness. Of the parkinsonian patients, 15 had at least 5 positive items on the RDC symptom checklist, a necessary, though not sufficient, criterion for a diagnosis of major depressive disorder.

The overlap has not been so extensively investigated in patients with primary depressive illness. The 30 patients with primary depressive illness in this study had a Webster rating intermediate between that of the parkinsonian patients and the normal controls. Each of the ten individual items contributed to the rating in the depressed patients, with the highest ratings for arm swing, facial expression and speech impairment. The only items with a mean rating per patient in the parkinsonian group of over twice that in the depressed group were tremor, rigidity, self-care and bradykinesia. The 12 depressed patients retested, whose mean depression rating had significantly improved, also showed a significant improvement in Webster rating. The Webster rating is a clinical one, but correlated with response times in the computerized testing in both groups of patients. Two of the depressed patients were taking neuroleptic medication (thioridazine) when tested, but the contribution of this medication to their motor disorder was not clear. One was tested while emerging from a depressive stupor during which she had been completely mute and akinetic. On retesting when clinically recovered and taking the same dose of neuroleptic, she showed a marked improvement in Webster rating. The other patient had initially been admitted to a neurological ward for investigation when he was noted to have a resting tremor, increased tone and difficulty initiating movements. At this time his only medication was a benzodiazepine. By the time he was tested, treatment for his depressive psychosis with an antidepressant and neuroleptic had been started, with improvement in both depressive symptoms and motor signs. These findings suggest a clinical overlap between affective and motor disorder in patients with primary depressive illness as well as in those with Parkinson's disease.

There have been two schools of thought on the relationship between motor and affective disorder. One school distinguishes sharply between neurological and psychiatric disorder, favouring psychological explanations of the psychiatric aspects of parkinsonism and motor aspects of psychiatric illness, and limiting the significance of the shared features of Parkinson's disease and depressive illness to the 'overscoring' it produces on depression rating scales in Parkinson's disease. The other school sees an intimate relationship between neurological and psychiatric disorder, regarding the psychiatric accompaniments of parkinsonism, and psychiatric illness itself, as manifestations of cerebral disorder, and more recently, in terms of dysfunction of common cerebral neurotransmitter systems.

Dysfunction of the mesocorticolimbic dopaminergic system has been demonstrated in Parkinson's disease, with the suggestion that, in this condition, loss of dopaminergic innervation in the prefrontal cortex could be the basis of akinesia and bradyphrenia, and in certain parts of the limbic forebrain, of affective disturbance (Price *et al.*, 1978; Javoy-Agid and Agid, 1980; Scatton *et al.*, 1982). Innervation of different structures by a single neurotransmitter system would explain the association between akinesia, cognitive impairment and depression in Parkinson's disease (Ajuriaguerra, 1971*a*; Agid *et al.*, 1984; Brown *et al.*, 1984). Psychomotor retardation, the most consistent feature characterizing major depressive illness (Nelson and Charney, 1981), may also be the result of dopaminergic dysfunction. Dopamine turnover, as measured by homovanillic acid concentration in the cerebrospinal fluid, is reduced in depressed patients with retardation but not in those without (van Praag *et al.*, 1975; Banki, 1977) and L-DOPA has a therapeutic effect on motor retardation in depressive illness without otherwise being an effective antidepressant (Goodwin *et al.*, 1970; Matussek *et al.*, 1970).

Experimental studies which have not supported the concept of bradyphrenia in parkinsonism (Worster-Drought and Hardcastle, 1924; Rafal *et al.*, 1984) have examined selected groups of patients, and have not considered the role of affective disorder or structural brain changes in this condition. Rafal and his colleagues pointed out that they could only conclude that slowing of cognition was not universal in Parkinson's disease nor obligatorily linked to bradykinesia, and felt that their study did not rule out the possiblity of bradyphrenia due to dopaminergic insufficiency in mesocorticolimbic pathways in some parkinsonian patients. This study supports that conclusion.

The parkinsonian patients in the present study were not specially selected. They were newly diagnosed, consecutively referred patients, satisfying the UK PDS brain bank criteria for a diagnosis of Parkinson's disease. They included patients with structural brain disorder and significant affective disorder. A measure of bradyphrenia was used which involved both cognitive processing and visual scanning. This measure suggested the presence of slowing of cognitive function in a proportion of the parkinsonian patients. This slowing was related to their motor impairment but behaved independently of this after treatment with dopaminergic agonists, suggesting that it was not entirely dependent on striatonigral function. In keeping with this was the relationship found between the measure of bradyphrenia and structural brain disorder mainly outside the basal ganglia. There was, furthermore, a relationship between the measure of bradyphrenia and affective impairment, which continued to hold after dopaminergic treatment. This supports suggestions of mesocorticolimbic dopaminergic disturbance in bradyphrenia and depression in Parkinson's disease. The same measure of bradyphrenia suggested slowing of cognitive function in a proportion of patients with primary depressive illness, associated with a mild but significant motor impairment in these patients. This was reversible with improvement in the affective disorder, and then coincided with a significant improvement in cognitive slowing. The findings of this study suggest a close relationship between bradyphrenia in Parkinson's disease and psychomotor retardation in depressive illness, first suggested over a century ago (Ball, 1882) and now finding a common basis in dysfunction of cerebral dopaminergic systems (Papeschi, 1972).

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APPENDIX

United Kingdom Parkinson's Disease Society Brain Bank Diagnostic Criteria for a Diagnosis of Parkinson's Disease

1. Bradykinesia, i.e., slowness of initiation of movement with progressive decrease of amplitude of movement.
2. At least one of the following:
   (a) 4–6 Hz rest tremor
   (b) rigidity
   (c) postural instability not due to primary visual, vestibular, cerebellar or proprioceptive deficits.
3. None of the following:
   (a) recent exposure to neuroleptic medication
   (b) past history of encephalitis, or oculogyric crises
   (c) past history of stroke, or stepwise course
   (d) toxin or designer drug exposure
   (e) cerebellar or pyramidal signs
   (f) early severe autonomic failure
   (g) supranuclear downgaze palsy
   (h) cerebral tumour or communicating hydrocephalus.

The 3 criteria must be met. The following support the diagnosis:
   (a) progressive illness
   (b) unilateral onset
   (c) persistent asymmetry of signs.

Brain (1987), **110**, 777-791

NATURAL HISTORY OF ASYMPTOMATIC EXTRACRANIAL ARTERIAL DISEASE

RESULTS OF A LONG-TERM PROSPECTIVE STUDY

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SUMMARY

The natural history of asymptomatic extracranial arterial disease (EAD) was studied prospectively in 339 patients admitted for serial ultrasound Doppler examinations. Annual mortality was high at 7%, but stroke mortality was low at 0.6%: 82 patients (24%) died during the follow-up period, which lasted up to seven years (median: 29 months), only 10 from stroke but 41 from cardiac causes. The risk of suffering a stroke without premonitory transient ischaemic attacks (TIAs) was similarly low at 0.4%. Progression of EAD was the only predictor established to indicate the individual patient's cerebrovascular prognosis among a series of criteria tested (age, sex, degree and extent of carotid and/or vertebral disease, risk factors and indicators of atherosclerosis). Deterioration of EAD was observed in 108 (36%) of 296 patients by repeated Doppler examination, 174 (59%) remained constant and 14 (5%) showed an improvement. The observed low rate of strokes without premonitory TIAs is not in favour for early carotid endarterectomy in the majority of neurologically asymptomatic patients.

INTRODUCTION

Despite the many developments in diagnosis for cerebrovascular disease, available therapy to affect the outcome once a stroke has occurred is still limited. Since extracranial carotid disease has been suggested as representing a major source of stroke, prophylactic treatment of patients with transient ischaemic attacks (TIAs) has been claimed to reduce the spontaneous stroke rate (Marshall, 1964; Fields *et al.*, 1970; Thompson *et al.*, 1970; DeWeese *et al.*, 1973). Carotid endarterectomy hence became one of the most frequent surgical procedures (Dyken and Pokras, 1984), although its value is still unproven as assessed by a controlled prospective randomized trial comparing surgically versus nonsurgically treated patients (Toole *et al.*, 1975; Sandok *et al.*, 1978).

Considering the increasing number of patients with asymptomatic extracranial arterial disease (EAD) detected by use of valid noninvasive methods such as

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Doppler ultrasound (Barnes *et al.*, 1981*b*; Pourcelot, 1982; Trockel *et al.*, 1984), regrettably less knowledge exists as to their appropriate management. This is primarily due to the continuing lack of information concerning the natural history of EAD. Interpretation of previous studies is restricted by (1) the retrospective nature of most series (Javid *et al.*, 1970; Humphries *et al.*, 1976; Cooperman *et al.*, 1978; Thompson *et al.*, 1978; Dorazio *et al.*, 1980; Levin *et al.*, 1980; Podore *et al.*, 1980; Wolf *et al.*, 1981; Durward *et al.*, 1982; Lindblad *et al.*, 1982); (2) selection of patients with mild obstructive lesions while others were treated surgically (Javid *et al.*, 1970; Thompson *et al.*, 1978; Moore *et al.*, 1978), or (3) recruitment of 'pseudo-asymptomatic' patients, who originally presented with TIAs or strokes, but revealed a contralateral carotid lesion in addition to the symptomatic one (Javid *et al.*, 1970; Humphries *et al.*, 1976; Johnson *et al.*, 1978; Levin *et al.*, 1980; Podore *et al.*, 1980; Durward *et al.*, 1982; Lindblad and Link, 1982). In addition, most series lack any information about the real vascular process when series were based on neck bruits only (Ziegler *et al.*, 1971; Cooperman *et al.*, 1978; Thompson *et al.*, 1978; Dorazio *et al.*, 1980; Heyman *et al.*, 1980; Barnes and Marszalek, 1981; Wolf *et al.*, 1981). Thus the important question has not yet been answered, namely whether or not the complication rate of any mode of treatment is less than the spontaneous risk of developing a stroke without premonitory TIAs.

PATIENTS AND METHODS

Serial Doppler examinations in 3225 patients admitted because of coronary artery disease (CAD) (n = 840, 26%), peripheral arterial disease (PAD) (n = 1620, 50%), bruits or risk factors for atherosclerosis (n = 765, 24%) revealed EAD in 339 patients without previous neurological signs or symptoms of a focal cerebral deficit. Diagnosis of CAD was made in patients with a history of myocardial infarction, repetitive angina and/or characteristic findings in the ECG or on coronary arteriography. PAD was diagnosed only as shown by peripheral arteriograms. Totals of 201 men and 138 women ranging in age from 39 to 80 yrs (mean 61.8 yrs) and 29 to 91 yrs (mean 62.8 yrs), respectively, entered the study. Most patients (n = 240, 71%) had PAD (n = 62, 18%), CAD (n = 81, 24%) or both (n = 97, 29%), including 92 patients (27%) with a history of myocardial infarction. Of these, 21 were treated by aortocoronary bypass and 35 by aortic-peripheral vascular reconstructions. The remaining patients (n = 99, 29%) were in good health. All were questioned about smoking (n = 184, 54%), hypertension (n = 201, 59%) diabetes (n = 78, 23%) and different forms of hyperlipidaemia (n = 128, 38%). Follow-up consisted of clinical and ultrasound investigations every 6 months and lasted up to 7 yrs (median: 29 months). Absolute endpoints for further analysis were death, the occurrence of TIAs, stroke, or extracranial endarterectomy. When a patient died, follow-up was accomplished by telephone interviews or correspondence with close relatives, local physicians and local hospitals, or by examination of the medical records. Because of the prospective design of this study, information about the vascular territory of neurological symptoms was available in all living patients and was only lacking in 2 who suffered a fatal stroke. Numbers of patients included over different periods were 339 (1 yr), 284 (2 yrs), 200 (3 yrs), 133 (4 yrs), 77 (5 yrs), 36 (6 yrs), and 14 (7 yrs) according to different individual intervals of follow-up. Only 1 patient defaulted (0.3%).

A directional continuous wave Doppler device was used for all recordings, the examiner being blind to the patient's clinical state. Classification of carotid and vertebral artery obstructions depended on the interpretation of the mean flow velocity curves recorded from the supratrochlear arteries, the vertebral arteries at the level of the atlas slope and at their proximal origin and from the carotid arteries (common, internal and external carotid arteries including the bifurcation). The parameters used for the assignment of carotid disease into five categories included peak frequencies, spontaneous flow direction, the shape of the waveforms and audible turbulences (Hennerici *et al.*, 1981; Barnes *et al.*, 1981*b*; Pourcelot, 1982; Trockel *et al.*, 1984): (1) normal and nonstenotic lesions (0–50%), (2) slight stenosis (50–70%), (3) moderate stenosis (70–80%), (4) severe stenosis (> 80%), and (5) total occlusion. From our recent series comparing noninvasive Doppler examination and angiography of 431 vessels in 333 patients the accuracy in separating each class of obstructive lesion is about 97% (Trockel *et al.*, 1984): sensitivities of the Doppler methods versus arteriography were 81% for slight, 93% for moderate, 86% for severe stenoses and 96% for total occlusions, specificities ranged at 99, 97, 98 and 98%, respectively. During follow-up, alterations of EAD were only considered if changes within these classes by at least one category were observed, to avoid overestimation of progression and regression. In patients who developed symptoms during follow-up, the duration of follow-up was measured from onset to the last examination before TIAs or stroke. In the vertebral system a subclavian steal phenomenon, severe proximal stenosis and hypoplasia were separated with great confidence (90% overall accuracy compared with angiography); 55 patients presenting either with a subclavian steal phenomenon (n = 46) or severe stenosis of the vertebral arteries (n = 9) were included without any early detectable carotid lesion and separately followed. Angiography was available in 35 patients and confirmed the Doppler results as classified.

Cranial computerized tomography (CT) had usually been performed at entry into the study. Patients with definite focal lesions were excluded although these defects might have been neurologically silent.

This study was not designed to investigate the effect of treatment on either the neurological or the vascular course of the disease. Hence patients treated particularly for EAD on a regular basis ought to be excluded. We could not, however, avoid some patients being treated at some time by their local physicians with acetylsalicylic acid (n = 86), combinations with dipyridamole and acetylsalicylic acid (n = 26), sulphinpyrazone (n = 1), ticlopidin (n = 1) or cumarines for coexisting PAD or CAD (n = 21).

Actuarial methods and life-table analysis were used to calculate the overall mortality, morbidity and vascular history during follow-up (Kaplan and Meier, 1958). Calculations to examine the influence of a series of factors and indicators on the progression of the disease were based on the proportional hazard regression model (Cox, 1972; Kalbfleisch and Prentice, 1980). Additional statistical procedures included the Student's t test, the sign test, and the χ^2 test. Most of the statistics were calculated using BMDP programs (BMDP1F, 1L, 2L).

RESULTS

A total of 339 neurologically asymptomatic patients with evidence of EAD entered the study between 1978 and 1982. EAD affected one vessel in 229 patients and two or more arteries in 110 patients (Table 1). With respect to the carotid arteries, 199 had slight or moderate stenoses, 36 severe stenoses and 49 patients already showed occlusions of the internal carotid artery (Table 2). At the time of the final examination (December 1984), 238 patients were alive, 82 were dead, 18 patients had undergone carotid endarterectomy while still asymptomatic and 1 patient was lost to follow-up (drop-out ratio = 0.3%).

Survival Probabilities and Causes of Death

The majority of patients died from cardiac causes (n = 41, 50%). Only 10 patients (12%) suffered a fatal stroke. Although some of them might have ignored TIAs before their fatal stroke, all were noted as strokes to avoid underestimation of the calculated stroke risk. Nine patients (11%) died of cancer and 18 (22%) of other

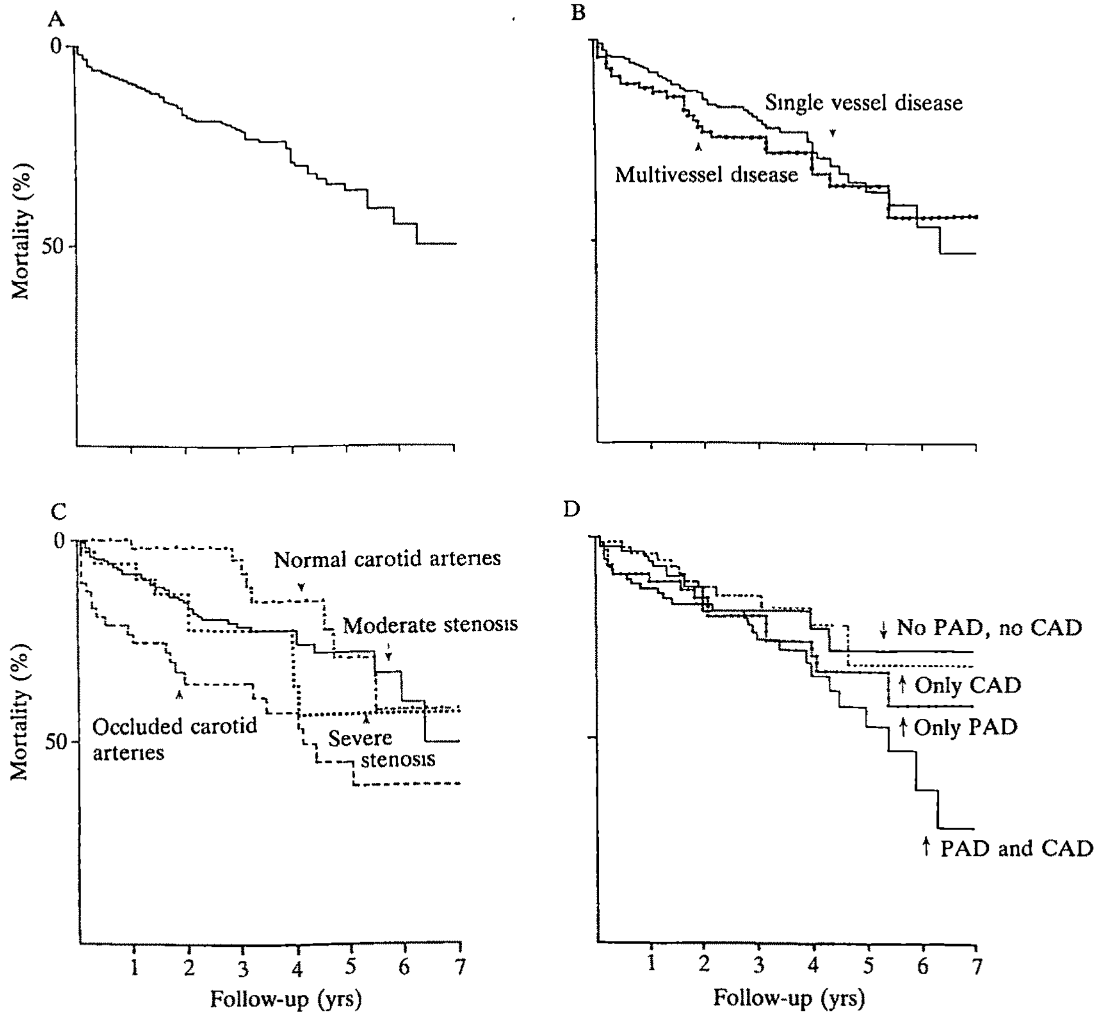

FIG. 1. Mortality rates after initial Doppler demonstration of EAD in 339 neurologically asymptomatic patients. A, total population; B, patients with single vessel and multivessel disease; C, patients with carotid occlusion, severe carotid stenosis, mild/moderate carotid stenosis, and normal carotid arteries but severe vertebral flow abnormalities. D, patients with prevalence of carotid artery disease (CAD), peripheral arterial disease (PAD), PAD and CAD, or neither.

diseases (e.g., subarachnoid haemorrhage, pneumonia, pulmonary embolic disease, renal insufficiency). In 4 patients (5%) the cause of death could not be established. Thus the overall annual mortality rate by life-table analysis was 7% at 7 yrs (fig. 1A), whereas the annual stroke mortality was only 0.6%.

Mortality rates differed with regard to the degree of EAD and manifestations of generalized atherosclerosis: patients with single vessel disease and multivessel disease had only slightly different survival probabilities with an insignificant tendency to a higher mortality rate of the latter group (Mantel Cox, $P > 0.30$)

(fig. 1B). Patients with occlusions of the carotid arteries, however, had a poorer prognosis (Mantel Cox, $P < 0.05$) than those with mild/moderate stenoses or normal arteries as shown in fig. 1C and Table 2. Finally, patients with combined PAD and CAD had the highest mortality and those with neither had the best survival rates (fig. 1D). The prevalence of CAD and PAD did not differ significantly between the subgroups with differing EAD involvement (χ^2 test, $P > 0.05$); thus our mode of patient recruitment did not bias the distribution of different degrees of initial EAD according to the prevalence of PAD and CAD.

The high cardiac mortality rate was not due to a disproportionally high incidence of cardiac deaths in patients who at entry into the study already had CAD or developed angina and/or myocardial infarction during follow-up: among the 41 patients who died from cardiac causes (29 male and 12 female), 22 had signs or symptoms of CAD including 14 with a history of recent myocardial infarction, while 19 were cardiologically asymptomatic initially. A similar prevalence of CAD and myocardial infarction (54% and 34%) was found in the total series (53% and 27%). Moreover, only 5 patients suffered cardiac deaths among 104 who developed angina and/or myocardial infarction during follow-up.

TABLE 1. NATURAL HISTORY OF 339 PATIENTS WITH DIFFERENT DEGREES OF EXTRACRANIAL ATHEROSCLEROSIS

	Single vessel disease	*Multivessel disease*	*P*
No. of patients	229	110	
Female:male	1:1.3	1:2	n.s.*
Mean age (yrs)	62.1	62.3	n.s.**
Mean follow-up (mos)	33.3	30.4	n.s.**
Mean annual mortality rate	7.8%	6.7%	n.s.*
Percentage of strokes	5.7%	3.6%	n.s.*
Percentage of TIAs	7%	9%	n.s.*

* $P > 0.05$ (χ^2 test). ** $P > 0.05$ (t test).

Clinical Course of Surviving Patients

Eighteen patients had to be excluded from further analysis after carotid endarterectomy at a still asymptomatic stage. Progression of EAD observed during a mean period of 15.4 months preoperatively did not differ from that seen in the total population. Among the 238 patients remaining alive, 205 (87%) were asymptomatic, 26 reported TIAs (10%) and 7 (3%) had had a stroke without premonitory TIAs. CT scans available in 5 of the latter showed ischaemic lesions in 4 and a pontine haemorrhage in 1. No significant differences in age and sex distributions were found among these groups of asymptomatic and symptomatic patients. The combined annual stroke rate, irrespective of death or survival, was 0.97%, the annual stroke mortality was 0.6% and the annual stroke morbidity 0.4% (fig. 2).

Three of the 26 patients who reported TIAs developed a stroke after exclusion from the study (1 immediately after vascular surgery, which was performed in 10), which produces a 1.2% total annual stroke rate (fatal and nonfatal), if stroke had been selected as the only end-point of the study.

The prognosis of patients with severe bilateral carotid stenosis (> 80%) is of particular interest as is the natural history of those who developed total occlusion from a severe stenosis during follow-up. First, among 16 patients with bilateral severe carotid stenoses (9 men and 7 women, mean age = 61.8 yrs), followed for a mean of 35 months, 11 remained asymptomatic irrespective of the history of EAD; 4 died due to cardiac disease but only 1 suffered a stroke. Secondly, only 1 of 13 patients developed a stroke (8 men and 5 women, mean age 61.2 yrs, mean period of follow-up 33 months), who at reexamination showed progression of a severe stenosis (> 80%) to total blockage. Another patient reported TIAs, and 11 remained asymptomatic (2 later died from cardiac disease and 2 from diseases different from stroke).

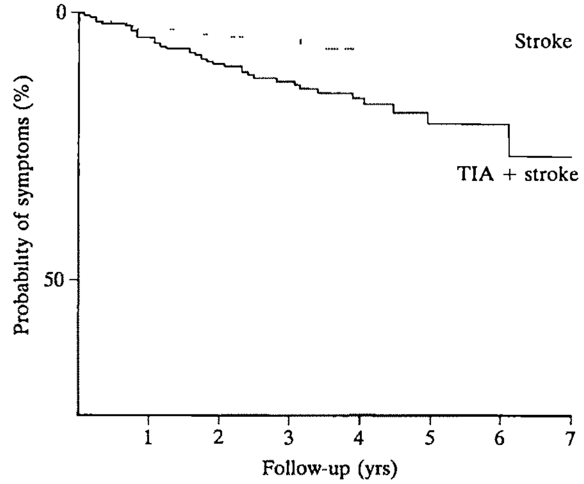

FIG. 2. Morbidity of sudden strokes vs that of both TIAs and strokes after initial Doppler demonstration of extracranial arterial disease in 339 neurologically asymptomatic patients.

In the long term, however, patients with carotid occlusion (n = 49) had a poor prognosis. Followed for an average of 30.2 months, 6 patients suffered strokes of which 4 were within the vascular territory of the occluded artery; 5 patients developed TIAs, 4 of which were ipsilateral to the occluded vessel. In addition, the annual mortality rate was high at 10.5%, cardiac causes representing the major sources of death (Table 2).

In contrast to what might have been suspected, patients who initially presented with pure vertebral disease displayed an incidence of cerebrovascular events similar to that noted in patients with carotid disease, although follow-up was even longer

TABLE 2. NATURAL HISTORY OF 339 PATIENTS WITH DIFFERENT DEGREES OF EXTRACRANIAL ATHEROSCLEROSIS

	Mild/moderate carotid lesions (50–80% stenosis)	*Severe carotid lesions (> 80% stenosis)*	*Carotid occlusions*	*Subclavian steal phenomenon/severe vertebral stenosis*
		P	*P*	*P*
No. of patients	199	36	49	55
Female·male	1 1.2	1 1.4 n.s *	1 5 1 < 0.05*	1.1 3 n.s.*
Mean age (yrs)	62.7	61.7 n.s.**	61 5 n.s.**	60 2 n s **
Mean follow-up (mos)	32.3	28.9 n.s.**	30.2 n s **	37 5 n s **
Mean annual mortality rate	6.2%	7.4% n s *	10.5% n s *	5.7% n s *
Percentage of strokes	2 0%	8 3% < 0.05*	12 2% < 0 05*	7 3% n s *
Percentage of TIAs	7.5%	5 6% n s.*	10.2% n s *	7.3% n s.*

* χ^2 test. ** t test. n.s. = not significant at $P > 0.05$ level

(Table 2). Furthermore, patients with combined carotid and vertebral disease were not at a higher cerebrovascular risk than those with pure carotid obstructions.

Vascular Territories and Types of Cerebrovascular Events

The correspondence between cerebrovascular events and vascular disease was significantly closer for late than for initial EAD as summarized in Table 3 (χ^2 test, $P < 0.025$). Patients who suffered a fatal stroke are not included because their later vascular process could not be established. Furthermore, most of the lesions initially detected in arteries where vascular territories corresponded with late symptoms were only minor (8 slight stenoses), 5 unilateral subclavian steal phenomena and 2 proximal vertebral stenoses. One patient had a severe stenosis in the carotid siphon and 4 already had a total occlusion of the internal carotid artery at entry into the study. Only 2 patients of the total study developed cerebrovascular events which could be attributed to moderate stenoses (70–80%) diagnosed at entry into the study and hence might have been prevented by early surgical treatment.

Although patients with single vessel disease did not differ significantly from those with multivessel disease in terms of mortality during follow-up, symptomatic patients tended to show multivessel disease more frequently than asymptomatic

TABLE 3. CORRESPONDING CLINICAL AND DOPPLER RESULTS IN 33 PATIENTS ALIVE WITH LATE PERMANENT (n = 7)/TRANSIENT ISCHAEMIC EVENTS (n = 26)

Vascular territories involved	*Initial EAD*		*Late EAD*	
	Corresponding	*Noncorresponding*	*Corresponding*	*Noncorresponding*
Carotid left	9	6	14	1
Carotid right	6*	5	9*	2
Vertebrobasilar	7	1	7	1
Total	22 (64.7%)	12 (35 3%)	30 (88 2**%)	4 (11 8**%)

* One patient is counted twice because of bilateral hemisphere TIAs and bilateral carotid lesions

** Significant at $P < 0\ 025$ level (χ^2 test) patients: 56% of those who later developed TIAs or strokes showed a definite progression of EAD which was observed in only 30% of those who remained asymptomatic (χ^2 test, $P < 0.005$). This is probably due to the different progression of EAD in both subgroups, since symptomatic and asymptomatic patients did not differ in the degree and extent of their initial vascular process. A marked difference was observed when late EAD was considered where there was a higher incidence of two and three vessel disease in symptomatic cases and a lower percentage of single vessel disease as compared with patients who were still asymptomatic (χ^2 test, $P < 0.025$).

TABLE 4 FOLLOW-UP OF CAROTID ARTERY DISEASE IN 296 PATIENTS (592 CAROTID ARTERIES)

		Late Doppler results				
Early Doppler results		*Normal* (< 50%)	*Mild stenosis* (50–70%)	*Moderate stenosis* (70–80%)	*Severe stenosis* (> 80%)	*Occlusion*
Normal (< 50%)	373	322	31	13	4	3
Mild stenosis (50–70%)	97	8	62	16	11	—
Moderate stenosis (70–80%)	44	—	—	39	3	2
Severe stenosis (> 80%)	41	1	—	—	27	13
Occlusion	37	—	—	—	—	37

Course of EAD

In contrast to the clinical findings, the extent of progression of EAD was rather severe. A review of serial studies on 296 patients who could be reexamined at least once, revealed that 174 (59%) were unchanged, 14 (5%) improved and 108 (36%) showed disease progression. The latter consisted either in deterioration of the degree of stenosis (n = 39, 36%) (Table 4), involvement of additional vessels (n = 50, 46%) or both (n = 19, 18%). Progression of EAD occurred more frequently in symptomatic than in asymptomatic patients as shown in fig. 3A: the mean annual rate of progression of 12.7% on a 6-year basis in still asymptomatic patients is significantly lower (Mantel Cox, $P < 0.005$) than the 22.5% progression rate in symptomatic patients based on a 4-year observation time; even on a 7-year basis this difference would be significant (20.0%). However, the latter calculation is less confident due to the small number of subjects who became symptomatic after a 6 or 7-year symptomless interval.

Risk Factors and Indicators of Atherosclerosis

As indicated in Table 5, failure time analysis, including methods relying on the proportional hazard regression model, were used to study whether progression of

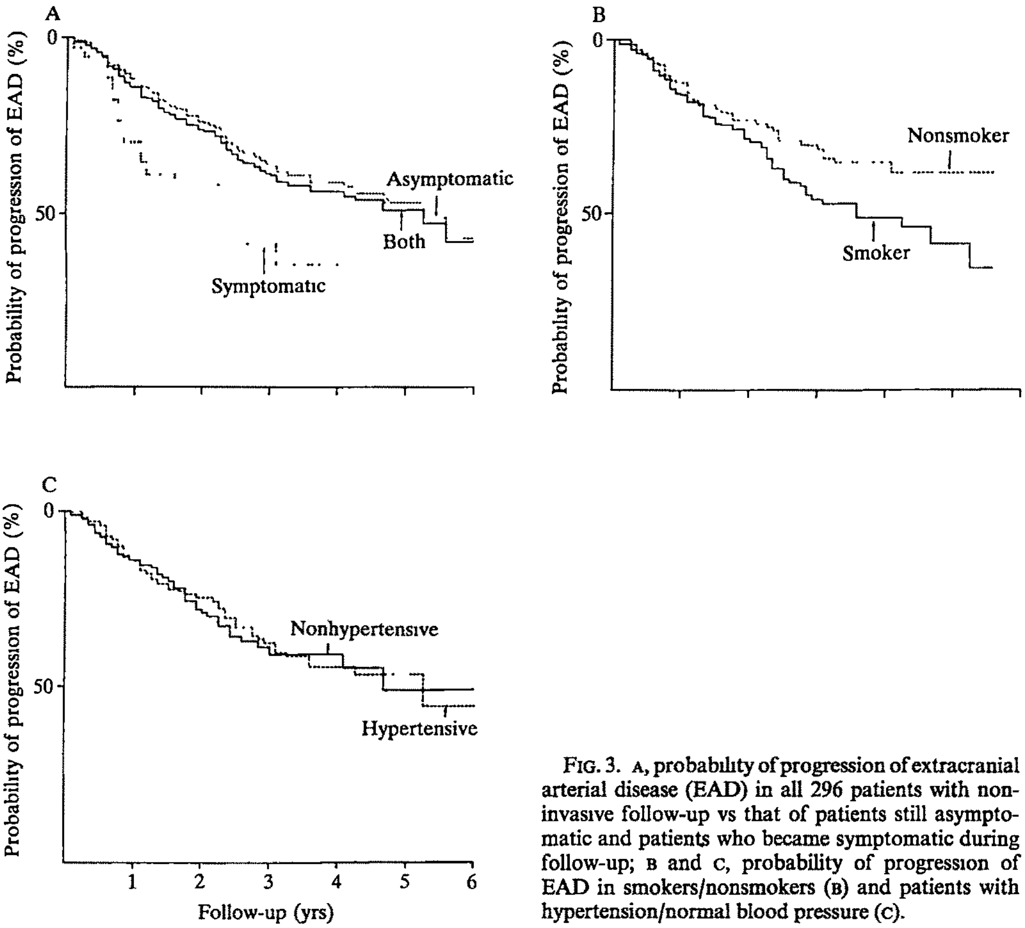

FIG. 3. A, probability of progression of extracranial arterial disease (EAD) in all 296 patients with non-invasive follow-up vs that of patients still asymptomatic and patients who became symptomatic during follow-up; B and C, probability of progression of EAD in smokers/nonsmokers (B) and patients with hypertension/normal blood pressure (C).

TABLE 5 PROPORTIONAL HAZARD REGRESSION MODEL FOR PROGRESSION OF EAD VS RISK FACTORS

Variables	*First step*	*Second step*	*Third step*
Covariates	(—)	(Smoking)	(Smoking/PAD)
Sex	0.2144	0.4118	0.7052
Age	0.4573	0.1465	0.2344
Hypertension	0.7455	0.7327	0.5493
Smoking	0.0387*	0.0387	0.1456
Diabetes	0.1086	0.1391	0.2942
Hyperlipidaemia	0.4109	0.5577	0.8655
Obesity	0.2182	0.1924	0.2715
Positive family history	0.2464	0.2120	0.2554
PAD	0.0153*	0.0536*	0·0536
CAD	0.1462	0.0644*	0.1289

* Indicates variables to be taken in the next step P to enter 0.1, P to remove 0.15. PAD = peripheral arterial disease. CAD = carotid artery disease

EAD was influenced by various risk factors or indicators of atherosclerosis: introduction of various variables (age, sex, history of high blood pressure, smoking habits, diabetes, hyperlipidaemia, obesity, positive family history of stroke, PAD and CAD) in the step-wise Cox regression model leads to selection of PAD and smoking at a significant level (P to enter 0.1, P to remove 0.15) as a result of the partial maximum likelihood criterion. Since both parameters are significantly correlated (χ^2 test, $P < 0.001$; contingent coefficient $CC = 0.42$, corrected for maximum contingency according to Pearson), we further evaluated the influence of smoking abuse as a sole covariate. This resulted in the additional significance of both PAD and CAD for the model. Inclusion of both PAD and smoking as covariates performed in a third step achieved the following conclusions: (1) a significant description of progression of EAD (global χ^2 test, $P < 0.02$); (2) smoking habits remained a significant variable apart from being associated with PAD. All other independent risk factors and indicators did not improve the model significantly.

DISCUSSION

This study was designed to examine the natural history of EAD that involved significant obstruction in the arteries supplying the brain (> 50%) in neurologically asymptomatic patients. Such lesions can be detected reliably by the noninvasive Doppler methods used and may be classified according to different degrees of stenosis at an overall accuracy of 97% compared with arteriography (Barnes *et al.*, 1981*b*; Hennerici *et al.*, 1981; Pourcelot, 1982; Trockel *et al.*, 1984).

After a long-term follow-up of 339 patients prospectively selected from 3225 patients during a seven-year period the principal results now presented indicate the following. (1) A low annual risk of stroke without premonitory TIAs at 0.97%, reflecting particularly low annual stroke mortality and morbidity rates (0.6% and 0.4%, respectively). This is in favour of a considerably higher rate of TIAs among all patients who developed cerebrovascular events (2.5% annual rate). (2) A high cumulative mortality, which mainly results from the cardiac death rate being four times higher than that of strokes (50% vs 12%). Although the overall mortality rate correlates with the degree of carotid disease (normal < stenosis < occlusion), the number of extacranial vessels involved (single vessel disease < multivessel disease) and the prevalence of manifest atherosclerosis outside the cerebral arteries (CAD < PAD < both), these parameters are, like bruits, indicators of the extent of atherosclerosis as a general disease rather than predictors of an individual cerebrovascular risk. (3) The only parameter associated with the development of cerebrovascular events in patients with asymptomatic EAD is progression of vascular disease: the atherosclerotic process remained constant in 70% of patients who were still asymptomatic during follow-up as compared with only 44% of those who experienced TIAs or strokes. Moreover, symptoms are more closely associated with late usually more severe vascular lesions than the initial ones: only 2 among 339 patients who entered the study had more than 50% carotid stenosis, which was probably responsible for the late cerebrovascular event and might have been prevented by early endarterectomy.

Cigarette smoking proved to be the only ordinary risk factor and the prevalence of PAD the only indicator of atherosclerosis being significantly associated with progression of EAD. Smoking contributed in particular, apart from being in itself associated with PAD. The lack of a significant covariation between the risk factors examined and progression of EAD might at least partly be due to the recruitment and classification of risk factors in our series. However, risk factors, which are well known to be associated with an increased risk for generalized atherosclerosis (e.g., hypertension, diabetes and hyperlipidaemia) show a significant correlation (χ^2 test, $P < 0.05$) with the prevalence of the peripheral vascular process, although they do not obviously influence progression of EAD. As to the question of EAD progression, the prevalence of PAD and/or CAD, correlating significantly with and hence summarizing the effect of these risk factors, might be a better indicator for the presence of a pathogenetic process responsible for EAD deterioration than most of the single risk factors.

Our results confirm preliminary observations (Barnes *et al.*, 1981*a*; Hennerici *et al.*, 1982; Roederer *et al.*, 1984; Chambers and Norris, 1984) of a low stroke rate without preceding TIAs in asymptomatic patients with EAD, although these studies differ in many aspects. Barnes *et al.* (1981*a*) followed 72 patients with asymptomatic carotid disease after coronary or peripheral artery revascularization up to two years (mean 11.3 months). Continuous-wave Doppler methods were used when considering > 50% carotid stenoses. Whereas 12 patients became symptomatic, only 1 suffered a stroke without premonitory TIAs, 10 reported TIAs and 1 had a stroke with prior TIAs probably not recognized; thus the mean stroke rate in this series was about 1.4%. Preliminary data on 500 patients followed for up to 30 months by Chambers and Norris (1984) suggest an annual stroke rate well below 0.5%. Although their results are not yet published in detail, these authors reported 28 ischaemic events; 26 were TIAs and only 2 strokes, most of them in patients with stenosis of > 75%. Roederer *et al.* (1984) reported 3 strokes without premonitory TIAs in a series of 162 patients followed for up to three years (mean interval not indicated). One was associated with the finding of an internal carotid artery already occluded at the initial exmination, the others were associated with progression of an initially < 50% lesion to a severe stenosis and of a moderate stenosis to total occlusion respectively. The annual stroke rate without premonitory TIAs hence was similarly low at about 1%. Comparison of their data with ours and with the aforementioned series is, however, limited by a considerably different mode of patient recruitment and methodology: they included only 21 (6%) haemodynamically significant carotid lesions (> 80%) in favour of small carotid lesions (n = 202, 62%) producing less than 50% lumen reduction. Such lesions are, however, difficult to separate from normal conditions on the basis of the haemodynamic parameters used (Zarins *et al.*, 1981, 1983; Reneman *et al.*, 1985). Since high-resolution ultrasound devices (> 7.5 MHz) were not available, they probably included an unknown number of subjects with normal carotid arteries by preferential use of a single-gate Doppler instrument for patient selection. Despite such differences, the similarity of the results with respect to the very low incidence of strokes without prior TIAs is striking. Nevertheless, such findings are probably not representative of all patients in a general population with newly diagnosed EAD elsewhere. In our study significant EAD was most frequently found in patients with PAD, CAD or at least risk factors for atherosclerosis, but rarely occurred in healthy subjects (Hennerici *et al.*, 1981). Although mortality rates were very high in our series, they might be smaller in another trial. However, since the risk for strokes without preceding TIAs was similarly low for different degrees of EAD, our mode of recruitment was unlikely to have influenced the major observation of a low risk for sudden strokes in all patients with asymptomatic EAD.

It would have been interesting to compare directly the results of this study with those of a prospectively followed control group including subjects of similar age, sex, risk factors, PAD and/or CAD but without EAD at Doppler examination. Unfortunately any idea of realizing such a project had to be abandoned because of the intrinsic difficulties in recruiting and following a similarly large group of patients at a reasonable level of compliance: (1) patient selection for the present series was already difficult, being based on an annual Doppler examination rate of as many as 3,000 patients since 1978; (2) strict criteria for a definite diagnosis of CAD or PAD included angiographic examinations; (3) regular reexamination twice a year in this long-term prospective series with a very low drop-out rate was thought to be necessary for a definitive data analysis. Therefore interpretation of the present data lacks the comparison with the natural history of EAD from its earliest onset in a population, for example, in the absence of any detectable carotid and/or vertebral lesion, but it is at least based on the best that is available.

Since the risks from the spontaneous course of the disease do not reach the surgical risks of endarterectomy recently reported (mean operative mortality of about 1.8% and morbidity of about 4.3% (Long *et al.*, 1985)), our data suggest that carotid endarterectomy is inadvisable for the majority of asymptomatic patients. Whether or not a subgroup of patients particularly at risk of developing a stroke may benefit from surgery, such as young patients with a reasonably good life-expectancy in the absence of CAD who demonstrate rapidly progressive, haemodynamically significant carotid stenoses, remains to be seen. This particular group of patients may benefit from carotid endarterectomy even at an asymptomatic stage for two reasons. First, internal carotid artery occlusion is shown not to represent a stable condition in the long term but to carry the highest risks both for permanent and transitory cerebrovascular events. Secondly, once a severe stenosis has advanced to total occlusion, surgical restoration of normal carotid flow is limited and bypass procedures obviously are without clinical benefit (EC/IC Bypass Group, 1985).

Our present results should not anticipate further randomized trials with patients treated surgically and nonsurgically. They may, however, be important for the design of such studies and a final comparison between any form of treatment and the spontaneous history of the disease.

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FACIAL FLUSHING AND SWEATING MEDIATED BY THE SYMPATHETIC NERVOUS SYSTEM

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SUMMARY

Sweating and flushing of the forehead and cheeks in response to body heating, embarrassment and strong gustatory stimulation were investigated in 23 patients with a unilateral lesion in the sympathetic pathway to the face. A lesion anywhere along this pathway impaired thermoregulatory sweating and flushing on the denervated side of the forehead in most patients and also of the cheek in some cases. Emotional sweating was also diminished on the denervated side of the forehead irrespective of the site of lesion, but impairment of emotional vasodilatation was noted only with peripheral (second or third neuron) lesions. These findings suggest that sympathetic vasodilator fibres accompany vasoconstrictor and sudomotor fibres through conventional sympathetic pathways to the face. Gustatory sweating and flushing were symmetrical in most patients but flushing was more marked on the denervated side in three cases. Gustatory sweating was accompanied by flushing on the denervated side of the forehead in one patient following section of the T2 and T3 roots.

It is concluded that the cervical sympathetic outflow is the main pathway for thermoregulatory flushing and emotional blushing and that diminution or absence of such vasodilator reactions is a usual component of Horner's syndrome unless the responsible lesion is confined to the first thoracic root. Gustatory vasodilatation and sweating is preserved and becomes exaggerated in some instances.

INTRODUCTION

The anatomical pathways concerned with facial sweating are understood more clearly than those responsible for flushing. Sudomotor fibres destined for the face may arise from the eighth cervical down to the fourth thoracic root, but the major contribution is from T2 (Goetz, 1948). Postganglionic fibres ascend adjacent to or surrounding the external and internal carotid arteries before joining peripheral branches of the trigeminal nerve with which they are distributed to the skin (List and Peet, 1938). In patients with Horner's syndrome whose lesion is distal to the bifurcation of the common carotid artery, impairment of sweating is confined to the medial aspect of the forehead and side of the nose (Morris *et al.*, 1984). In more proximal lesions, apart from brachial plexus injuries sparing the roots below T1, loss of sweating involves the complete half of the face. Impairment of sweating was

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found to be variable after a central sympathetic lesion but was hemifacial in 2 of 5 patients (Morris *et al.*, 1984). Sudomotor fibres destined for the forehead therefore travel with sympathetic ocular fibres along the internal carotid artery, whereas the remainder of the face is innervated by fibres from the sympathetic plexus surrounding the external carotid artery. Sweating persists in the central mask of the face after cervical sympathectomy and is attributed to autonomic fibres passing in the greater and lesser superficial petrosal nerves to the sphenopalatine and otic ganglia (Monro, 1959). Some patients develop gustatory sweating on the ipsilateral forehead after cervical sympathectomy. The fibres responsible reach the forehead with the terminal branches of the trigeminal nerve but their origin is uncertain.

Facial flushing may be caused by release of sympathetic vasoconstrictor tone or by an active vasodilator mechanism, with one or other mechanism predominating in different facial areas. Blair *et al.* (1961) blocked cutaneous nerves supplying the ear and cheek with a local anaesthetic agent in human subjects and observed release vasodilatation in the ear but not the cheek. During body heating, the temperature of the nerve-blocked and normal ears did not increase further while temperature of the nerve-blocked cheek rose less than on the normal side, indicating that an active vasodilator pathway had been interrupted. Similar experiments conducted by Fox *et al.* (1962) enabled them to divide facial areas into those in which vasomotor control was mediated principally by variations in vasoconstrictor tone (ear and lip) and those in which it depended on active vasodilatation (scalp, forehead, chin and submandibular areas). Both mechanisms appeared to play a part in regulating circulation in the skin overlying the nose, but no conclusion was reached about the innervation of the cheek for technical reasons. Some reports suggest that cervical sympathetic fibres may be responsible for vasodilatation as well as vasoconstriction. After body heating, only the intact side of the face was observed to flush in several patients who had been subjected to unilateral cervical sympathectomy (Lewis and Landis, 1930; Hyndman and Wolkin, 1941). Emotional blushing was also said to be impaired on the sympathectomized side in one patient (Lewis and Landis, 1930).

Another active vasodilator mechanism, studied in the external carotid circulation of the cat, is mediated by the greater superficial petrosal (GSP) nerve and the sphenopalatine and otic ganglia (Lambert *et al.*, 1984) with release of vasoactive intestinal polypeptide (VIP) as the peripheral transmitter agent (Goadsby and Macdonald, 1985). This vasodilator reflex, initiated by stimulation of the trigeminal nerve and brainstem nuclei such as the locus coeruleus (Gonzalez *et al.*, 1975; Lambert *et al.*, 1984), increases extracranial blood flow and skin temperature. The persistence in cats of some vasodilator activity on trigeminal stimulation after section of the trigeminal root suggests that antidromic impulses in the trigeminal nerve could also cause facial flushing, possibly through release of substance P or serotonin which are known to be present throughout the trigeminal system (Moskowitz, 1984). This may account for the facial flush seen during thermocoagulation of the trigeminal ganglion in man, primarily in regions rendered analgesic by the operation (Drummond *et al.*, 1983).

It thus appears that at least four mechanisms could be involved in facial flushing. The first results from a reduction in sympathetic tonic vasoconstriction in certain areas such as the ears and lips; the second may involve sympathetic vasodilator fibres in other areas such as the forehead; the third, which depends upon the GSP nerve and release of VIP, may be activated reflexly by excitation of trigeminal pathways; the fourth may depend upon the antidromic release of substance P or serotonin from trigeminal terminals.

In the present study, we investigated facial sweating and flushing in patients with a unilateral lesion in the sympathetic pathway to the face. We aimed to determine whether an intact sympathetic nervous system was necessary for facial flushing and sweating in response to body heating, embarrassment and powerful gustatory stimulation.

METHODS

Patients

Twenty-three patients with a unilateral lesion in the sympathetic pathway to the face were studied. The subjects' informed consent for all procedures was obtained. Twenty-one patients showed pupillary signs of Horner's syndrome and were separated, according to diagnosis, into groups with probable lesions of the first, second or third sympathetic neuron. Five patients with first neuron lesions had brainstem infarcts and another patient had a congenital Horner's syndrome with heterochromia iridis and preservation of the ciliospinal reflex. Four of 5 patients with second neuron lesions developed Horner's syndrome after unilateral preganglionic sympathectomy while the fifth had an avulsion injury of the brachial plexus after a motor cycle accident. Three of 10 patients with third neuron lesions had an aneurysm of the internal carotid artery, another 6 had a residual Horner's syndrome after cluster headache, and 1 after thyroidectomy. Instillation of two drops of 2% tyramine (which releases noradrenaline) into each eye confirmed that the lesion was preganglionic for 9 of 11 patients with probable lesions of the first or second neuron because the pupils dilated symmetrically after 30 min. One patient was not tested because of glaucoma and the other patient, with a brainstem infarct, responded less on the denervated side. This patient had undergone surgery after a middle ear infection on the side of the Horner's syndrome which possibly damaged postganglionic sympathetic fibres in the caroticotympanic plexus (Walsh and Hoyt, 1969). Nine of 10 patients with suspected third neuron lesions showed a smaller pupillary response to tyramine on the denervated side; the other patient was not tested because of glaucoma. A symmetric response to the instillation of two drops of 5% cocaine (which blocks the reuptake of noradrenaline) in each eye confirmed the presence of normal pupillary sympathetic innervation in 2 other patients whose second and third thoracic roots had been sectioned on one side.

Procedures

The experiment was carried out in an air conditioned laboratory maintained at 22 ± 1° C. Capillary pulsations were detected with reflectance photoplethysmographs (Narco Bio-Systems) attached with adhesive washers to the forehead 2 cm above the eyebrows in line with the pupils, and to the anterior part of the cheeks 3 cm below the eyes. Pulsations were recorded on a Narco Bio-Systems Mark IV Physiograph. The room air conditioner was switched off while sweating was measured with a ServoMed Evaporimeter EP1. The measuring head was held against the forehead 1 cm from the midline above the eyebrows, starting on the right side, and then 4 to 5 cm above the eyebrows 2 cm from the midline. Because statistical analyses detected no difference in response between these two sites, only the former measure is reported. The measuring head was held against the skin until a steady reading was obtained (usually 20–30 s). Between each measurement, a fan was used to blow residual water vapour out of the measuring head. To protect the sensor elements of the Evaporimeter from sweat and grease, a stainless steel grill (part no. 2107) was placed over the measuring head when in operation. Output from the Evaporimeter was written out on the Narco Bio-Systems Physiograph for later analysis.

Responses to embarrassment, gustation and heating were measured in fixed order because it was expected that recovery would be slower after heating than after embarrassment or gustation; 5 to 10 min were generally required for responses to return to baseline.

To induce embarrassment, the subject was asked to sing children's songs ('Baa-Baa Black Sheep', and 'Old MacDonald had a Farm'). These songs were tape-recorded and played back while physiological measurements were carried out, starting with vascular pulsations to record the maximum response, and then sweating. Most subjects reported at least slight embarrassment during this procedure: mean rating on a 10 cm visual analogue scale ranging from 'not at all' embarrassed (0) to 'extremely' embarrassed (10) increased from a pretest level of 0.2 to 3.7 during the test ($P < 0.001$).

To induce gustatory reactions, the subject held one-half of a teaspoon of Tabasco sauce (manufactured from chillies) in the mouth for 30 s or until it was swallowed. Vascular pulsations were then recorded until vasodilatation was maximal, after which sweating was measured. Tabasco sauce produced a burning sensation in the mouth which gradually subsided over the next 5 to 10 min.

To induce thermoregulatory responses, sheets, blankets and plastic covers were draped around the subject's body, leaving the head uncovered. A fan-forced heater circulated hot air under the covers. Facial sweating was observed 8 to 65 min (mean 30 min) later, after which measurements began. In the body heating experiments vascular pulsations usually reached a maximum after sweating measurements had been completed.

Amplitude of capillary pulsations in each site was measured for 30 s before each test, and for 30 s during the peak response. Because the recorded amplitude of vascular pulsations was influenced by individual characteristics such as the thickness and opacity of skin overlying cutaneous vessels, pulse amplitude during tests was converted to percentage change from pretest levels for statistical analyses. For sweating, the change from pretest levels during each test was analysed statistically. The change in sweating was not converted to a percentage of baseline because this inflates the magnitude of change from low baselines. When used without the protective grill over the measuring head, output from the Evaporimeter is read in $g \cdot m^2 \cdot h^{-1}$. Because the grill altered this calibration by reducing the area of measurement, rate of evaporation is reported here in arbitrary units. Pretest levels averaged 10 units. Sweating usually became visible at a reading of 40 units, and values rarely exceeded 60 units. Sjaastad *et al.* (1981) reported that facial sweating is visible at 90 $g \cdot m^2\ h^{-1}$ when the Evaporimeter is used without the protective grill although, because of instrument characteristics, this value probably underestimates the true rate of evaporation (Wheldon and Monteith, 1980). Despite problems of calibration, the *relative* rate of evaporation from different areas of the body can be assessed accurately with the evaporimeter (Wheldon and Monteith, 1980).

Analyses of variance were used to determine whether the site of the sympathetic lesion influenced facial sweating and vascular responses. These analyses had one between-groups factor (site of lesion) and one within-groups factor (denervated versus intact side).

RESULTS

Analyses of pretest levels did not detect any difference between the denervated and intact sides or any correlation with site of lesion for sweating or vascular measurements.

Thermoregulation

A lesion anywhere along the sympathetic pathway to the face impaired thermoregulatory sweating and dilatation of skin vessels on the denervated side of the forehead (*see* Table). Heating was continued until sweat was visible on the forehead in all patients; clinical inspection and Evaporimeter measurements (fig. 1) confirmed that sweating was diminished on the denervated side in most cases. For patients with third neuron lesions, asymmetry of sweating was greatest in the supraorbital region—beads of sweat were seen to extend across the upper one-third of both sides of the forehead in 7 of 10 patients.

TABLE. FACIAL SWEATING AND VASCULAR DILATATION IN HORNER'S SYNDROME ON THE DENERVATED AND INTACT SIDES[1]

	Mean change (SD)		*Response asymmetry*	
	Denervated side	*Intact side*	*F ratio*[3] *(1, 18 df)*	*P*
Body heating				
Forehead sweating	+17[2] (11.8)	+36[2] (5.6)	47.53	< 0.001
Forehead pulsation	+21% (65%)	+173%[2] (151%)	22.29	< 0.001
Cheek pulsation	−5% (27%)	+34%[2] (66%)	7.47	< 0.05
Embarrassment				
Forehead sweating	+10[2] (10.7)	+14[2] (10.6)	7.94	< 0.05
Forehead pulsation	+24%[2] (28%)	+43%[2] (49%)	5.42	< 0.05
Cheek pulsation	+22%[2] (22%)	+29%[2] (37%)	1.15	—
Taste of chillies				
Forehead sweating	+7[2] (7.9)	+7[2] (9.8)	0.05	—
Forehead pulsation	+21%[2] (34%)	+15%[2] (23%)	0.48	—
Cheek pulsation	+5% (16%)	+12% (30%)	1.31	—

[1] The degree of sweating is shown in arbitrary units, for reasons given in the text, while changes in capillary pulsation are shown as percentages. [2] Significantly different from pretest level. [3] For difference between changes on the intact and denervated sides.

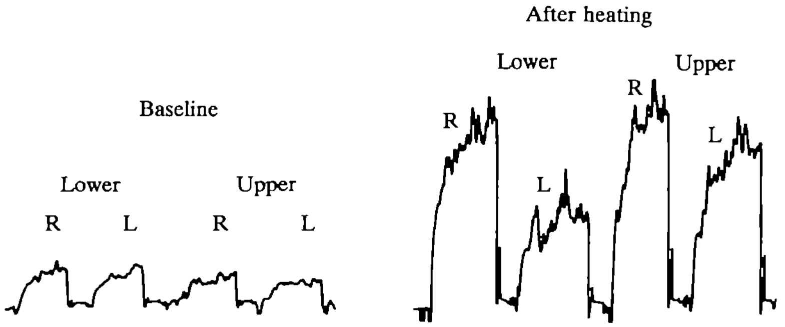

FIG. 1. Relative rate of evaporation from the forehead before and after body heating in a patient with left-sided Horner's syndrome.

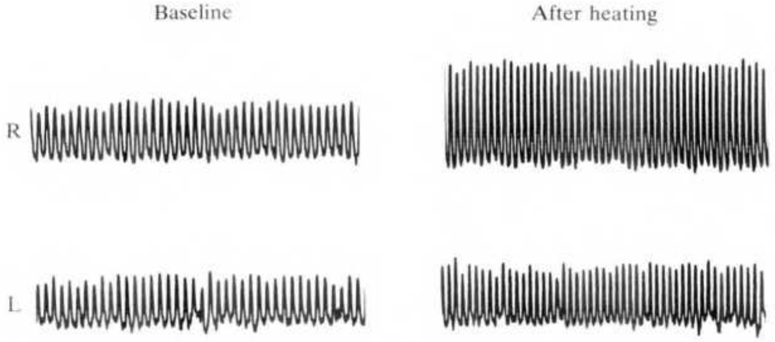

FIG. 2. Pulse amplitude from the forehead before and after body heating in a patient with left-sided Horner's syndrome.

At the onset of sweating, vascular dilatation was greater on the intact side of the forehead (fig. 2) in every case except for the patient with an avulsion injury limited to the first thoracic root, who showed a symmetric increase in pulse amplitude. In some patients a distinct flush was present on the intact side of the face, extending to a sharp line at the midline of the forehead, whereas the denervated side of the face remained pale and dry (fig. 3). Statistical analyses indicated that dilatation of skin vessels was impaired on the denervated side of the forehead irrespective of the site of lesion. Third neuron lesions distal to the bifurcation of the common carotid artery impaired vascular dilatation mainly on the medial aspect of the forehead while the lateral aspect sometimes flushed normally.

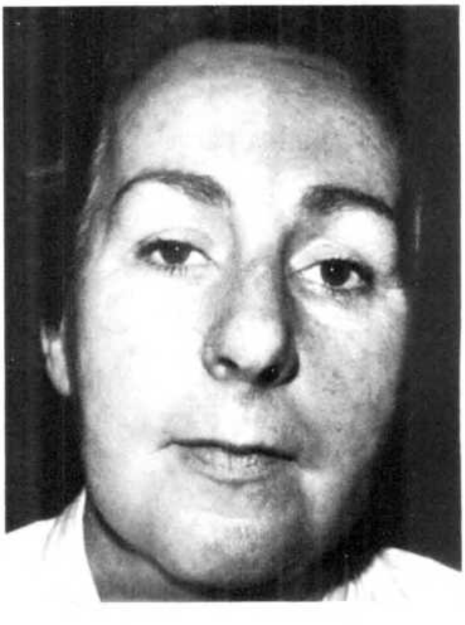

FIG. 3. Absence of thermoregulatory facial flushing on the side of Horner's syndrome after cervical sympathectomy.

Maximum dilatation of blood vessels in the forehead preceded that of the cheeks by up to 30 min. Only those patients who were heated for more than 30 min developed asymmetry of pulse amplitude in the cheeks (mean −11% on the denervated side compared with +57% on the intact side). The importance of the duration of heating time was confirmed by statistical analysis (interaction between heating time and degree of pulse amplitude asymmetry in the cheeks, F(1, 19) = 4.60, $P < 0.05$). Flushing of the cheek on the denervated side was impaired in 3 patients with lesions of the third sympathetic neuron (2 patients with cluster headache and 1 postthyroidectomy). Sweating was also impaired ipsilaterally in 2 of these patients and was not observed on either cheek in the other patient.

Emotional Sweating and Blushing

Although sweating and blushing during embarrassment were usually not great enough to be visible, the increases in sweat production and pulse amplitude were statistically significant in all regions and were significantly greater on the intact side of the forehead (*see* Table). Vascular dilatation was greater on the intact side of the forehead for patients with lesions of the second or third sympathetic neurons (a mean of +46% compared with +16% on the denervated side), but not for patients with first neuron lesions (interaction between site of lesion and asymmetry of response, F(2, 17) = 3.48, $P = 0.054$). In the latter group, pulse amplitude increased symmetrically (43% on the denervated side and 37% on the intact side). No other relationship between the extent or asymmetry of response and site of lesion, or rating of degree of embarrassment, was detected.

Gustation

Tasting Tabasco sauce caused small but significant increases in sweating and pulse amplitude on both sides of the forehead (*see* Table), the degree being unrelated to the site of the sympathetic lesion. Sweating was visible on the denervated side of the forehead in 1 patient and on the intact side of another, both third neuron lesions. Significant asymmetry of vascular dilatation in the forehead was observed in the first case and in 2 other patients with third neuron lesions: pulse amplitude increased by 42, 95 and 108%, respectively, on the denervated side but remained virtually unchanged on the intact side.

Section of T2 and T3 Roots

Thermoregulatory sweating and flushing was impaired on the denervated side of the forehead in both patients with unilateral section of the T2 and T3 roots. Both patients sweated freely on the intact side of the forehead but not on the denervated side. Pulse amplitude increased 96 and 260%, respectively, on the intact side of the forehead, compared with increases of 4 and 22% on the denervated side.

Emotional sweating was also impaired on the denervated side of the forehead in both patients. Vascular dilatation during embarrassment was diminished on the denervated side in 1 patient: pulse amplitude increased 45% on the intact side of the forehead and only 23% on the denervated side.

Tasting Tabasco sauce induced visible sweating on the denervated side of the forehead in 1 patient and no change in the other. Increases in pulse amplitude were greater on the denervated side of the forehead in both patients, increasing 68 and 43%, respectively, compared with no change and a decrease of 11% on the intact side.

DISCUSSION

Standard texts and monographs pass lightly over the mechanism of facial flushing. Baljet and Groen (1985) stated that blushing is generally considered to be due to postganglionic sympathetic cholinergic innervation but that 'a significant anatomical basis for a vasodilator mechanism in blushing has not so far been established'. In the same symposium on the subject, van der Meer (1985) commented that vasodilatation of the skin is at least partly an active process although 'the mechanism of blushing is still largely unknown'.

Because reactive vasodilatation sometimes develops immediately after cervical sympathectomy, it has been assumed that the dominant effect of the sympathetic nervous system is one of vasoconstriction. Johann Horner in 1869 described vasodilatation as a part of the syndrome that was subsequently named after him (Fulton, 1929). During discussion of the case of a woman aged 40 years with a right ptosis and miosis, Horner recorded that 'the right side of her face became red and warm, the colour and heat increasing in intensity under our observation, while the left side remained pale and cool' (Fulton, 1929). The present study shows that Horner's case must have been atypical, possibly resulting from a progressive irritative lesion, because flushing is usually impaired as much as sweating, at least in response to body heating. Of our 21 cases of Horner's syndrome, thermoregulatory flushing was diminished on the side of the sympathetic lesion in 20, the exception being a man with avulsion of the brachial plexus sparing the second thoracic root. Photoplethysmography demonstrated a diminished response to embarrassment although few patients blushed visibly to the relatively bland stimulus of singing childish songs. Impairment of blushing on the sympathectomized side has previously been described by others (Lewis and Landis, 1930; Haxton, 1948). In the present study, emotional vasodilatation, measured by capillary pulse amplitude, clearly showed a lesser response on the side of a second or third neuron lesion. The response was symmetrical in first-order neuron lesions, suggesting that there are alternative central pathways for emotional blushing. Emotional sweating was diminished on the denervated side of the forehead in patients with central as well as with peripheral sympathetic lesions.

Two patients whose second and third thoracic roots had been sectioned showed impairment of sweating and flushing on the denervated side similar to those patients who also had the ocular component of Horner's syndrome. Thus fibres which regulate facial sweating and flushing emerged from the spinal cord through the second and third thoracic roots in these 2 cases. Symmetric thermoregulatory responses in 1 patient with a lesion of the first thoracic root indicates that the majority of sudomotor and vasomotor fibres passed through other rami in this instance. There is some individual variation in the point of emergence of sudomotor fibres from the spinal cord. Goetz (1948) reported that section of the first and second thoracic roots abolished facial sweating in 60% of patients. In the remaining cases additional sympathetic innervation was thought to originate from C8, T3 and T4.

Intrinsic vascular tone is thought to increase shortly after sympathectomy to compensate for the loss of neural regulation of tone. This leaves open the possibility that facial flushing in subjects with an intact sympathetic nerve supply is caused by a reduction in vasoconstrictor outflow. However, the demonstration by Blair *et al.* (1961) and Fox *et al.* (1962) of the presence of active cutaneous vasodilatation in the forehead, cheek and chin, in combination with the present findings, suggests that vasodilator fibres accompany vasoconstrictor and sudomotor fibres through conventional sympathetic pathways to the face. The earlier onset of flushing and sweating on the forehead than the cheeks indicates that the forehead is more densely innervated by such sympathetic fibres.

Whether sympathetic nerves initiate cutaneous vasodilatation directly or indirectly remains unresolved. In patients with congenital absence of sweat glands, body heating does not stimulate active cutaneous vasodilatation on the forearm (Rowell, 1983). However, sweat gland activity is not the only requirement for flushing because the hands and feet, which sweat readily, do not show active cutaneous vasodilatation. Furthermore, 3 of our patients with Horner's syndrome sweated symmetrically across the forehead although vascular dilatation was diminished on the denervated side. Hypersensitivity of denervated blood vessels to circulating vasoconstrictor substances could theoretically have impaired facial flushing in patients with postganglionic lesions, but not in patients with more proximal lesions. In most patients, areas which did not sweat readily also did not flush, but the dissociation between these two functions in a few patients suggests that sweating and flushing are controlled by different fibres or depend upon different transmitter substances released from the same fibres.

Clinical observation of sweating on the cheeks and forehead confirmed that loss of sweating was usually confined to the medial aspect of the forehead in patients with sympathetic lesions distal to the bifurcation of the common carotid artery (Morris *et al.*, 1984). Diminution of thermoregulatory flushing was confined to a similar area, indicating that vasomotor fibres destined for the forehead probably branch from the sympathetic plexus surrounding the internal carotid artery. In cluster headache, Horner's syndrome is thought to be caused by repeated dilatation of the internal carotid artery in the carotid canal which damages the plexus of sympathetic fibres surrounding the artery (Vijayan and Watson, 1982). Impairment of flushing (2 patients) and sweating (1 patient) on the cheek as well as the forehead on the denervated side suggests that the lesion is sometimes proximal to the common carotid artery bifurcation, or that sympathetic fibres surrounding the external carotid artery sometimes suffer damage as well as those travelling with the internal carotid artery.

Physiological gustatory sweating is symmetric and is usually confined to the central mask area of the face (Lee, 1954; Monro, 1959). Gustatory sweating is accompanied by facial flushing, salivation, lacrimation and nasal secretion (Lee, 1954). This response persists after interruption of cervical sympathetic nerves and is thought to be mediated by parasympathetic fibres travelling with the facial or glossopharyngeal nerves (Monro, 1959). Our finding that gustatory sweating and flushing were symmetrical in most patients with Horner's syndrome supports the view that this response is not mediated by cervical sympathetic nerves.

Three main types of pathological gustatory sweating have been described, the first being termed idiopathic, and the other two developing after cervical sympathectomy, preganglionic or postganglionic (the latter involving sympathetic fibres accompanying peripheral branches of the trigeminal nerve) (Drummond *et al.*, 1986). Gustatory sweating and flushing on the denervated side of the forehead in one of our patients after section of the second and third thoracic roots resembled the preganglionic syndrome. The same symptoms in a few patients (flushing in 3 and sweating in 1) with lesions of the third neuron may correspond to the postganglionic syndrome. In contrast, gustatory sweating was impaired on the denervated side of the forehead in 1 other patient with a third-order neuron lesion, indicating that sudomotor fibres participating in the gustatory response originated in the superior cervical ganglion or joined the sympathetic trunk proximal to it in this instance.

In conclusion, thermoregulatory facial flushing and emotional vasodilatation and sweating were found to be mediated by conventional cervical sympathetic pathways, whereas gustatory sweating and flushing were usually unaffected by a lesion in the sympathetic pathway to the face. The consistency of impairment of thermoregulatory facial flushing on the denervated side in Horner's syndrome indicates that the measurement of facial flushing after body heating could be used to confirm the diagnosis in equivocal cases.

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BOOK REVIEWS

Multiple Sclerosis (Butterworths International Medical Reviews, Volume 6). Edited by W. I. McDonald and Donald H. Silberberg. 1986. Pp. 193. London: Butterworth. Price £25.00.

The editors of this volume of the Butterworths International Medical Reviews series in Neurology, devoted to multiple sclerosis, have set out in just under 200 pages a very readable and succinct account of recent advances. The book as a whole will provide practising neurologists with a highly informative and balanced review, aspects of which will also be of special interest to other professional groups involved in the assessment and care of people with this disease. There are 10 chapters, devoted in turn to diagnosis, imaging, epidemiology, genetic factors, immunological abnormalities, pathogenesis, pathophysiology, neuropsychological aspects, treatment and symptomatic management. The 14 contributors, from both sides of the Atlantic, are leading experts in their respective fields. Notwithstanding the difficulties associated with producing any general text on this subject, the editors are to be commended on achieving their stated objective of leading 'from the process of diagnosis, incorporating modern methods of assessment, through descriptions of aetiological and pathogenetic factors and the pathophysiology of the disease to specific information about the management of patients'.

From the point of view of the clinician, the most obvious change of the last decade is the increasing use of different types of investigation (evoked responses, CT, immunochemistry) for earlier diagnosis. There has been a shift from the complete reliance on clinical features as exemplified by the Schumacher Committee criteria (1965) to the schemes, discussed here by McDonald and Silberberg in their chapter on diagnosis, being devised to take account of the application of these new techniques. The review of imaging methods in multiple sclerosis clearly gives pride of place to use of MRI with its high resolution of white matter lesions and superior ability to display the brainstem and spinal cord. We are reminded, however, of differential diagnosis and of the need for follow-up to determine the prognostic significance of subclinical radiological abnormalities. While 'multiple lesions' may indeed be demonstrable at the time of an initial monosymptomatic presentation, the temptation to equate this with multiple sclerosis should be resisted. In this context, the editors' statement that diagnosis 'finally depends on the clinical behaviour of the disorder in the individual patient over time' means that, in the absence of a disease-specific test, the empirical formula of 'dissemination in place and time' retains its central position in the diagnostic process.

The chapter on epidemiology of multiple sclerosis includes a summary of twin data. The conclusion that such surveys have identified the operation of an environmental factor is clearly argued but the valid rider that further population-based studies are unlikely to define this factor highlights the need for new approaches to the search for an aetiological agent or agents. The basis for genetic predisposition (HLA studies) is reviewed with commendable brevity and thoroughness. Review of immune mechanisms (Lisak) is an eclectic and very well-researched article (179 references) that deserves to be widely read. In terms of assessment and management, the chapter on neuropsychological and psychiatric disturbances focuses much needed attention on the questions of cognitive decline and affective disorders in multiple sclerosis, as well as the occurrence of psychiatric phenomena in relation to chronic neurological disease. The review of treatment aimed at modifying the course of the disease suggests that immunosuppressive therapy does appear to help some people with multiple sclerosis but that conclusive evidence based on controlled trials is still lacking. The account of symptomatic management is helpful and sets out a useful concept of primary, secondary and tertiary effects to describe, respectively, direct neurological symptoms, physical complications and 'psychological, social, and vocational ramifications' of the disease.

Space prohibits comment on all the contributions in turn, which have been skilfully combined. The book clearly serves to illustrate the scope of current research in multiple sclerosis. Priority is given to developments that appear to be of most practical significance. There is the hope that new ability to recognize and to monitor the disease in early stages will indeed lead to fresh concepts of aetiopathogenesis and rationalization of therapy. The present volume fully maintains the high standard already set in this series under the general editorship of C. D. Marsden and A. K. Asbury and is a very welcome addition to the literature on multiple sclerosis.

J. F. HALLPIKE

Neonatal Neurology. Second edition. By Gerald M. Fenichel. 1986. Pp. 342. Edinburgh: Churchill Livingstone. Price £36.00.

Although 50 pages longer, I found the second edition of this book less satisfactory than its predecessor which seemed sharp and up to date. Since no new chapters have been added the previous topics have been amplified somewhat but not to a degree which reflects the rate of progress of the subject. For example, we now recognize the ultrasound appearances (incidentally there are almost no ultrasound reproductions in this edition) and the generally poor prognosis of periventricular leukomalacia. A considerable amount of work has been done on anterior and middle cerebral artery flow using Doppler ultrasonography which is not adequately discussed. Magnetic resonance imaging, which is likely to become increasingly important, and magnetic resonance spectroscopy, which provides information about brain phosphocreatine reserves, are not mentioned. The disproportionate space given to the newer congenital myasthenic syndromes, while interesting, reflects lack of balance since they are so rare.

Although cheaper than its rivals in this field, it is now also less competitive; the prospective purchaser would be well advised to dig a little deeper in his pocket to find the extra.

R. O. ROBINSON

Subacute Sclerosing Panencephalitis: A Reappraisal. Edited by F. Bergamini, C. A. Defanti and P. Ferrante. Excerpta Medica International Congress Series 691. 1986. Pp. 422. Amsterdam: Elsevier. Price Dfl. 220.00.

This volume includes the papers and posters presented to the Second International Symposium on SSPE held in Bergamo in May 1985. There are 2 introductory presentations, 37 papers, and 12 posters, describing epidemiology, clinical features and investigation, the results of treatment, aspects of pathogenesis and immunology and virology of this ubiquitous condition. The contributions come from America, Europe West and East and the Mediterranean Littoral; they range from substantial clinical series to single case reports.

The main message is that immunization against measles reduces the incidence of SSPE, and by this means it may be possible to eradicate the condition.

I found the book irritating to read because the typeface changes from paper to paper; the English is frequently eccentric; and little editing has taken place, resulting in needless repetition. There is an index of authors but no index of contents; and the volume is very expensive. I think it is likely to be acquired only by those who attended the Symposium.

MILNE ANDERSON

Developmental Psychobiology and Developmental Neurobiology. *Handbook of Behavioural Neurobiology Volume 8.* Edited by Elliott M. Blass. 1985. Pp. 328. New York: Plenum. Price $55.00.

Recent advances in techniques that allow ever more detailed descriptions of cellular and molecular changes in development have not bypassed neuroscientists. Indeed it must appear to some that the data obtained by these new methods will soon overwhelm other areas of neuroscience and the study of behaviour will not only be the poor relation but in danger of becoming extinct. The articles in this book provide testimony to the fact that a multidisciplinary approach, including the analysis of behaviour, when used to study developmental problems, can be both exciting and rewarding. The potential reader should not be put off by the title; 'psychobiology', as I understand it in this context, is the study of behaviour, 'neurobiology' the study of the physiology and cellular biology of the nervous system. This book provides a meeting point for many subdisciplines that do not often come together in the same journals or at the same congresses. A dominant theme throughout the book is to make clear that the developing organism is not just a miniature adult but has particular behaviours that change in response to the environment and that underlying cellular events go hand in hand with the behavioural changes.

This book contains eight chapters covering a wide variety of topics. Oppenheim and Haverkamp review the development of the embryo from a behavioural and cellular perspective. The temptation to think of behaviour as a postpartum event is clearly inadequate and they draw on a wide range of experiments to link behaviour and cell biology. It is an interesting and thought-provoking chapter. Fentress and McLeod address the issue of the development of motor patterns and highlight the diversity of motor patterns in the developing organism and how these are sculpted in development to attain their adult form. Moran deals with two behaviours peculiar to the neonate, suckling and huddling. Understanding the complexity of these behaviours and the interactions between the neonate and its environment have made rapid advances in recent years. The relationship between neonatal physiology and these behaviours is well illustrated in this review.

The development of vocal learning in songbirds has been intensively studied in the last fifteen years to make an intriguing story. Although there are already a number of reviews of this subject the article by Bottger and Arnold is a useful addition. They show that this field has lost none of its impetus and convey the excitement that yet more fascinating discoveries lie just around the corner. Olfaction and taste are two sensory systems that all too often are only touched on in textbooks and reviews, and their development virtually ignored. This is surprising given their importance to the developing neonate. Pederson, Greer and Shepherd review the development of the olfactory system of the rat. They use examples from their own work to show how modern anatomical methods with a metabolic marker can demonstrate which neural pathways are involved in odour-guided behaviour in the developing rat pup. Mistretta and Bradley devote their chapter to a review of what is largely their own pioneering work on the developmental neurophysiology of the gustatory pathways in rat and sheep. The emphasis is again to relate these findings to developing behavioural responses, and the relationship between changes in sheep gustatory neurons and human infant behaviour is of particular interest.

The review by Hirsch on the developing visual system may appear to be an example of oversubscription to a well-reviewed field. However, this review does serve to illustrate what consequences abnormal environmental rearing can have on behaviour. It is clear that although there is a wealth of neurophysiological data there is a relative paucity of behavioural data and it is an important question as to whether some of the changes in the responses of single cells have any behavioural significance. The final chapter by Leon discusses the development of thermoregulation, the strategies for thermoregulation and the long-term consequences of early thermal experiences.

Although the chapters are diverse in the topics they cover and the approaches used, this is one of the strengths of the book. It should serve to bring to the forefront some areas that all too often make few of the headlines. This book is a most worthwhile purchase for libraries and all involved in the teaching of, or research on, the developing nervous system. Each chapter is largely self-contained but also well referenced and will serve as a useful source. Apart from its possible value as a reference book it is also full of fascinating information—a good read.

V. HUGH PERRY

Vascular Aphasia. By J. M. Tonkonogy. 1986. Pp. 220. London: MIT Press. Price £29.95.

The small book, *Vascular Aphasia*, is based on personal experience with autopsied clinical material. The literature review is somewhat selective and does not include some of the important recent contributions detailing the anatomical distinctions related to vascular disease and aphasia. The clinical examination and the autopsied material is descriptive and anecdotal, representing a personal experience in the style of classical neurologists experienced in higher cortical function. This book is of interest for specialists in aphasia and students of cerebral localization.

ANDREW KERTESZ

The Neurobiology of Down Syndrome. Edited by Charles J. Epstein. 1986. Pp. 258. New York: Raven Press. Price $51.50.

The application of recombinant DNA techniques, particularly those involved in gene mapping, has led to rapid advances in our knowledge of genetic disorders, including some of neurological significance such as Huntington's chorea. However, the precise identification of the affected gene(s) and a full understanding of the perturbations in phenotypic expression which result in the disease pathology has not yet been achieved.

In Down syndrome it has been known for many years that the underlying genetic defect is the presence of an extra copy of chromosome 21, resulting in the increased expression of a set of normal genes. Which particular genes are implicated in the pathological process has yet to be established (although it appears that triplication of only a segment of the chromosome may be sufficient). A book on the neurobiology of Down syndrome would appear to be timely, since a description of phenotypic changes and pathology should shed light on some of the genes involved and suggest candidate genes for further study. This book is based on the National Down Syndrome Society conference on the Neurobiology of Down Syndrome held in New York in 1985. There are two general sections: the first groups together chapters on the various clinical, neurochemical and neurophysiological alterations in Down syndrome, and the second loosely covers experimental approaches to the problem, including the mouse trisomy 16 animal model of Down syndrome as well as some basic studies on the structure and function of the nervous system.

The introductory chapter by the editor is particularly useful. It summarizes the gene dosage effects (both primary and secondary in the case of the interferon receptor) of genes localized to date on chromosome 21 and draws attention to the disproportionate effect on phenotype which could result from the over-expression of genes encoding regulatory proteins or indeed cell recognition molecules at critical periods of development.

Since this book is compiled from the individual contributions of participants at the Down syndrome conference it suffers from the limitations of many books of this type in that it is by no means comprehensive. There is also some inevitable minor repetition in the introductions to several chapters (which serves to emphasize salient points!). The Alzheimer type pathology associated with older Down's subjects is extensively covered in several chapters. However, little mention is made of the pathological segment of the long arm of chromosome 21 or of the minority of Down's cases arising as a result of translocation. Similarly, in the section on the mouse trisomy 16 model comparative mapping information on human chromosome 21 and mouse chromosome 16 and details of the trisomy 16 phenotype are scant. A more general introduction of this model system would be helpful. A description of this is included in the excellent review of Down syndrome in Charles J. Epstein (1986), *The Consequences of Chromosome Imbalance*, Cambridge University Press. A chapter on the nonneural correlates of Down syndrome including cardiac and immunological deficits, although not directly encompassed in the subject of this symposium, would also be a useful addition, since genes which are ubiquitously expressed may also be of relevance in the brain. Chapters in the second section which do not have a direct relevance to Down syndrome itself, for example those on cell–cell interactions and analysis of cloned brain genes, are nevertheless clearly written concise summaries.

In essence *The Neurobiology of Down Syndrome*, although not the comprehensive compendium that the title suggests, will be useful to workers who wish to familiarize themselves with progress being made in multiple disciplines relating to the alterations in brain structure and function in Down syndrome.

CHRISTINE HALL

Visceral Sensation. Edited by F. Cervero and J. F. B. Morrison. *Progress in Brain Research*, Volume 67. 1986. Pp. 324. Amsterdam: Elsevier. Price Dfl. 255.

I suspect that for many neurologists, at least clinical neurologists, visceral sensation is a subject about which their knowledge is at best hazy. Yet the sensory innervation of the heart, the lungs, the gastrointestinal tract and the bladder and reproductive organs, and how the sensations arising from them are processed are obviously of fundamental importance. It is not difficult to see why the subject of visceral sensation, important though it is, has received so little attention compared with the sensory innervation of the skin. For the clinician, investigation is obviously extremely difficult, the organs being internal and comparatively inaccessible, and for the patient, it is only in disease that the topic becomes of concern, since visceral sensations in health are innocuous and everyday phenomena: breathlessness during exercise, the sensations of hunger and thirst, and bladder and bowel fullness; cough and nausea may be occasional and barely noxious experiences. Whether sensations during sexual activity should be classified as visceral remains unclear.

Although largely neglected by clinicians, physiologists and pharmacologists have been increasingly turning their attention to the mechanisms of visceral sensation, and this book tackles the subject with the aim of assessing the major scientific advances that have occurred in the past few years. The editors have set out to achieve this 'state of the art' review by including both some of the contributions presented at a symposium on visceral sensation organized by the Physiological Society in 1985, and also contributions from others actively engaged in study of the subject. The editors have not fallen into the trap of merely publishing papers delivered at a meeting, but have truly fulfilled the editorial role by selecting and bringing together 15 first-class papers which are preceded by three introductory reviews: on some basic mechanisms of visceral sensations (Paintal), the clinical approach to visceral sensation (Procacci, Zoppi and Maresca), and afferent C-fibres and visceral sensation (Iggo). Following the three reviews, the second section contains 7 articles on visceral afferent systems, and the third section contains 8 articles on central nervous system mechanisms. Topics range from the neurochemistry of visceral afferent neurons to neural mechanisms of cardiac pain, and from vagal afferent innervation of the gastrointestinal tract to visceral inputs to sensory pathways in the spinal cord. Although clinical aspects do appear throughout the book, one is left in little doubt that recent advances have been scientific rather than clinical.

Each paper is written in an individual style and some duplication is present, but the editors fully achieve their aim of allowing the authors to express their views unhindered and to allow controversy. For example, the issue of referred pain is discussed by several authors (and more than appear in the Index): the importance of Ruch's convergence-projection theory is considered by Foreman and coworkers who also consider inhibition from visceral afferent input; central convergence and vicious circle mechanisms are thought important by Procacci and colleagues; the relevance of peripheral branching of visceral afferent fibres, some of which may supply both visceral and somatic receptors, is discussed by Willis and rather played down by Cervero and Tattersall, and the role of nonnociceptive input of adequate intensity in the absence of 'pain-blocking' inputs is postulated by Paintal. It is precisely these diverse approaches to the subject that makes the book so valuable, in addition to the factual presentations.

This book, containing important, scholarly and up-to-date reviews of a major and comparatively neglected subject, is outstanding. Contributors and editors are to be congratulated, as are the publishers, on the rapid appearance of such a well-produced text. The editors comment in the Preface that they 'are quite sure that a substantial number of the new observations reported in this volume will still form the core of a future publication in 10 years time'. I agree and much look forward to that future publication

G. D. SCHOTT

Anaesthesia and Intensive Care of Neurosurgical Patients. By Sheila M. Willatts and Frank J. M. Walters. 1986. Pp. 320. Oxford: Blackwell. Price £35.00.

This book, written by two well-respected neurosurgical anaesthetists from Bristol, is directed at the trainee in neurosurgical anaesthesia and fills the middle ground between an introduction to neurosurgical anaesthesia and comprehensive academic review of this speciality. The book starts with the only disappointing chapter. This attempts to cover the neuroanatomy of the central nervous system in 25 pages and could really have been omitted, since it is so succinct (the pons is described in three lines) that it could not have added anything to the knowledge of the reader. There follow chapters on the physiology relevant to cerebral ischaemia and the control of intracranial pressure, the investigation of cerebral function and neuropharmacology concerned in neurosurgical anaesthesia.

These chapters set the background to the main bulk of the book which covers many aspects of the anaesthetic management of the neurosurgical patient. Topics include neuroradiology, surgery for intracranial tumours, aneurysms, spinal surgery and postoperative care. There are additional chapters on paediatric neurosurgery, head injury management and neurosurgical pain-relieving procedures. The authors bring together the pathology, physiology, anatomy and pharmacology involved in a particular clinical situation and describe their personal approach to clinical management.

While I would not always agree with their methods, I liked their approach and it is obvious that the authors are speaking from personal experience. The novice looking for guidelines upon which to base his or her own practice will find this approach very useful.

The book is well presented in hardback and there are good clear illustrations. The text is not referenced but a list of key references is to be found at the end of each chapter This allows simple uncluttered prose but can also be frustrating. For example, I came across the following sentence 'A somewhat surprising but unconfirmed report using a mass spectrometer has calculated that the average volume of air embolized during an operation in the sitting position was 1400 ml' and was unable to trace the source.

L. LOH

Recent Advances in Neuropathology. Edited by J. B. Cavanagh. 1986. Pp. 167. Edinburgh: Churchill Livingstone. Price £30.00.

This is the third volume of *Recent Advances in Neuropathology* to provide up-to-date and critical reviews on issues of current importance in the rapidly expanding field of neuropathology. It is thinner in format than the preceding volumes from 1979 and 1982 and contains 7 chapters. The first chapter is an excellent review on new perspectives on glial cells by Mirsky and Jessen. In the section on intermediate filaments they conclude that the glial fibrillary acidic protein exhibits antigenic heterogeneity and is not restricted to astrocytes but shows a widespread and complex distribution among central and peripheral glia. Among the cell surface macromolecules, galactocerebroside is expressed also on nonmyelin-forming Schwann cells, suggesting that the glycolipid is not only a component in myelin sheaths but may also be involved in axonal-glial interactions. The interaction between the basal lamina and growing axons is beginning to be understood in molecular terms with the key molecules laminin and fibronectin promoting the elongation of PNS neurites. The evidence is that the macroglial cells of the rat optic nerves consist of two types: type 1 astrocytes which arise early in development and type 2 astrocytes and oligodendrocytes which differentiate from a common progenitor cell, is also reviewed.

Coakham and Brownell have critically reviewed the usefulness of monoclonal antibodies in the diagnosis of cerebral tumours and cerebrospinal fluid neoplasia. The panel of antibodies presently used for tumour diagnosis in Bristol is given, with examples of how they can significantly contribute to a correct diagnosis in quite a number of cases. They are particularly helpful in distinguishing lymphomas from other small round cell tumours in the brain. This is a rapidly expanding field and new generations of antibodies will soon appear including such that may recognize the presence of oncogene products in tissue sections.

Dyck and coworkers illustrate how their imaging system for nerve morphometry can be used to elucidate the underlying mechanisms of diabetic polyneuropathy. The arguments for a vascular versus metabolic cause of diabetic polyneuropathy are reviewed and by using their criteria for ischaemic nerve injury, that is, sufficient vessel alteration and characteristic nerve fibre pathology with central fascicular or sector fibre loss beginning at proximal levels and a mixture of axonal degeneration and segmental demyelination, they reach the conclusion that the lesions are compatible with an ischaemic neuropathy. The other chapters in the book review host resistance to gliomas (Bullard and Bigner), ultrastructural classification of pituitary tumours (Howath and Kovacs), neuropathies in domestic animals (Griffiths and Duncan) and the neuropathology of decompression sickness (Palmer).

To quote the editor, J. B. Cavanagh, this book shows how the active field of neurobiology inspires neuropathological research to understand the expression of diseases and disturbances in the nervous system. This is strongly emphasized by the first chapter on glial cells which in itself makes this volume worth acquiring.

Krister Kristensson

Progress in Neuropathology, Volume 6. Edited by Harry M. Zimmerman. 1986. Pp. 304. New York: Raven Press. Price $98.50.

Previous volumes in this series have been interesting and informative. This one is, overall, a disappointment. A collection of 14 articles each presents a personal view. They are of very diverse style and value. Perhaps the most 'neuropathological' chapter is that by Hirano and Llena on the parkinsonism-dementia complex of Guam and its comparison with both Alzheimer's and Parkinson's diseases. Similarities and differences are discussed, with an emphasis on neuronal tangles, and the review of the literature on the involvement or otherwise, in a wide range of neurological disease, of the basal nucleus of Meynert, is thought-provoking. It might be remembered, however, that very few neuropathologists have ever had the chance to look at one of the parkinsonism-dementia brains from Guam, and it may well be that this disease is on the wane. An article by Shu-Hui Yen and others is entitled 'Cytoskeletal abnormalities in neuropathology' and it, too, discusses neurofibrillary tangles. All sorts of neuronal pathologies are gathered together in this chapter, anything in which there is a tangle or inclusion composed of filaments. Such a lumping together may not be justifiable. The usefulness of haematoxylin and eosin in paraffin sections is emphasized! Is this progress? Of the other articles, 6 deal with theoretical and experimental aspects of tumours including 'Microtubules and regulation of cell growth' (D. H. Carney, W. C. Thompson); 'Tumour invasion and metastasis in the CNS' (D. A. Katz, L. A. Liotta), which discusses metastasis to the brain and the absence of metastasis by gliomas, the reasons for which remain unknown; human gliomas in culture are discussed in separate articles by J. S. Shapiro and by H. Cravioto and the experimental induction of tumours by JC virus is reviewed by Nagashima *et al.*; J. P. Bressler and P. L. Kornblith present their 'thoughts on the ontogeny of gliomas'—thoughts which are shared by many others. Other topics include a reevaluation of so-called 'neuron-specific enolase' which now seems to be quite nonspecific but has provided us all with a lesson of one sort or another. Muscle is given two chapters, one being a review of 'congenital myopathies' (H. Goebel), a nice review of a subject dominated by structural oddities and expressing scepticism about whether these structural abnormalities represent specific disease entities. The last article in the book is a very curious one indeed, being a paper on 'muscle involvement in fatal catatonia'

(G. F Walter, M. Minauf, E. Maurer) which seems to be the first appearance of this work, since the authors state that 'the muscle pathology in fatal catatonia has, to the best of our knowledge, not yet been investigated'. I believe an article of this sort might well not be acceptable as a refereed paper submitted to a good journal, and it seems unfair to the purchaser of a volume entitled *Progress in Neuropathology* to have included material which does not stand up to critical analysis.

Two other chapters are of considerably greater interest and represent growing points in basic and applied neuroscience. Lassmann and others present a review of the 'Characterization of inflammatory infiltrates in EAE' in which the contribution of newly produced antibodies to the identification of leucocytes is emphasized. A short article by E. A. Zimmerman on transplantation of neurons into the brains of animals deficient in hypothalamic hormones makes an interesting read. The first article in the book is by R. M. Sapolsky *et al.* and reviews work (mostly by the authors themselves) which purports to show an influence of glucocorticoids specifically on the hippocampus, enabling hippocampal neurons to survive a wide variety of insults ranging from hypoxia, through alcoholism, to old age. Mind-stretching stuff, this, requiring a good stiff drink while being read. Altogether a very mixed bag.

L. W. Duchen

Evoked Potentials. Edited by Roger Q. Cracco and Ivan Bodis-Wollner. *Frontiers of Clinical Neuroscience*, Volume 3. 1986. Pp. 564. New York: Alan Liss. Price $70.00.

Evoked Potential Primer. Visual, Auditory, and Somatosensory Evoked Potentials in Clinical Diagnosis. By Rainer Spehlmann. 1985. Pp. 400. London and Boston: Butterworth. Price £62.00.

The purpose of *Evoked Potentials*, edited by Roger Cracco and Ivan Bodis-Wollner, is to cover comprehensively data provided by evoked potential (EP) techniques in the field of clinical and basic neurophysiology. It contains 49 chapters written by 99 contributors, each of them giving an up-to-date report in their own field of research. In their preface, the editors insist on the fact that, by mixing in a single volume theoretical considerations on information processing, data from electrophysiological and pharmacological animal experiments and results of EP investigations in clinical neurology, they aimed at demonstrating the specific place of EPs at the frontiers of clinical neuroscience. They partly succeed and partly fail in accomplishing their ambitious enterprise.

The book is divided into eight sections: 'Methodology, Animal Models, Anatomy, Biochemistry and Pharmacology, Differential Diagnosis, Surgical Monitoring, Pediatrics and Cognitive Disorders across Ages.' There is obviously some degree of overlap between these categories and, as in Cortazar's novel *Hopscotch*, the book can be read by following the order of the chapters or by picking information from place to place to come to synthetic conclusions. The reviewer has experimented with both approaches and the latter proved to be generally more exciting, and practically the only one possible to make a reasonably short review of the contents. One of the reasons to choose parallel rather that linear processing to analyse this book is that the editors themselves seem convinced that multichannel processing of sensory information by the brain is a general rule; another is that the place of some chapters in one of the above categories is not always justified. For example the chapter by Cant and Shaw on 'Central somatosensory conduction time', based on data from routine and technically very conventional recordings of somatosensory evoked potentials (SEPs) in patients, is included in the section 'Methodology', whereas far-field SEP recording, which is the most recent refinement of the SEP techniques, is not discussed in this section but in two chapters, one by J. Desmedt, the other by Kimura *et al.*, in the section 'Anatomy'.

The most coherent and original aspect of the book is the new insight it gives to the EP approach of the visual system by means of 16 chapters which contain convincing evidence that visual evoked potentials (VEPs) and electroretinography (ERG) are often under-utilized in clinical testing. Neurologists will find in this bulk of papers useful information concerning the whole spectrum of VEP applications. The rationale for stimulating the eye with a sinusoidal grating pattern rather than with the usual checkerboard pattern is presented in a very didactic chapter on principles of physiology in VEP methodology by Bodis-Wollner *et al.* The importance of lateral interactions between retinal receptive fields for the choice of an appropriate visual stimulus is emphasized in a chapter by Zemon *et al.* Possible sources of the pattern ERG responses are discussed in two papers by Maffei and Fiorentini and by Sherman which do not fully elucidate the question as to whether pattern ERG has a preganglionic or a ganglionic origin in the retina. However, there is some evidence that, by using a pattern with appropriate luminance and contrast and spatial frequency, pattern ERG can give specific information concerning the underlying pathology in retinal and optic nerve diseases. Three chapters argue for the concept that VEPs might be useful for studying synaptic interactions and not simply for measuring conduction velocities. Bodis-Wollner *et al.* sum up their results showing that abnormal VEPs in Parkinson's disease are correlated with the dysfunction of the dopaminergic system; two animal studies by Zemon *et al.* and Kirby *et al.*, respectively, support the view that VEPs could be used as an index to investigate the function of the synaptic network of the visual cortex. The mechanism and the possible reversibility of VEP delays in demyelinating diseases are nicely discussed in an experimental study by Onofrj and Gambi. Macular sparing is identified as the main reason for failure of VEPs to detect some hemianopic field defects in a chapter by Celesia, in which results of positron emission tomography and VEPs are compared.

It is not easy to weld the chapters devoted to SEPs into a coherent entity; some of them only summarize well-known conclusions concerning the use of SEPs in clinical testing. They give the impression that there is a gap between recent methodological advances such as far-field SEP recording, detailed in the two above-cited chapters by Kimura and Desmedt, and routine techniques used in most laboratories of clinical neurophysiology. Data supporting the view that muscle 1A afferents contribute to the generation of scalp-recorded SEPs are reviewed in a chapter by Burke and Gandevia. This notion stresses the need for stimuli other than electric stimulation of mixed nerves to improve SEP exploration of the somatosensory system. A chapter by Pratt and Starr updates the results of SEP recordings obtained by natural forms of somatosensory stimulation. Elements of correlation between SEPs and single unit response to air-puff cutaneous stimulation in awake monkeys are given in a chapter by Gardner *et al.*

Auditory EPs (AEPs) have been neglected in this book; clinical papers on brainstem responses (BAEPs) have no originality, midlatency responses are not considered, and the only chapter on long-latency cortical EPs concerns cortical responses evoked by speech sounds in infants. Thus the neuropsychologist who seeks a review of AEP applications to the study of aphasia or of central auditory deficits due to focal brain lesions, as well as the neurosurgeon who wishes to know about the utility of BAEP monitoring during posterior fossa surgery, will certainly be disappointed.

Apart from the chapter by Halgren *et al.*, in which arguments concerning the generators of the P3 component are clearly presented (in spite of an obscure sentence without a verb on p. 272), papers on EP cognitive components are very traditional.

In the category 'miscellaneous', chapters by Haldeman on pudendal nerve evoked responses, by Rossini *et al.* on transcutaneous motor stimulation, by Elidan *et al.* on vestibular EPs and by Kauffman and Williamson on neuromagnetic field recording, are concise reviews of very specific fields.

The courageous aim of the two editors, which was to demonstrate continuity between basic sciences and clinical neurophysiology, is not fully achieved. However, this book contains a tremendous amount of scattered information and, by reading it, EP professionals who cannot afford the time to follow an increasing literature will update their conceptions and perceive some of the future trends of EP research. The reviewer definitely doubts whether inexperienced readers will consider it as an attractive introduction to evoked potentials.

Evoked Potential Primer complements Rainer Spehlmann's *EEG Primer* which has become a classic in the clinical neurophysiology literature. The title suggests that the book addresses itself mainly to beginners; in fact with 1562 references cited in the text and 92 illustrations, this volume is to be viewed as a compact or 'pocket' Evoked Potential Encyclopedia in which trained neurologists and neurophysiologists might also find useful information. The book enters into competition with two former comprehensive reviews which have recently covered the field of EP applications to clinical medicine (Halliday, 1982, and Chiappa, 1983). It differs, however, from its competitors in two main points: first, the section on EP recording methods is larger than in any other previous publication, secondly, the section devoted to somatosensory evoked potentials (SEPs) avoids any rigid or dogmatic positions concerning recording methodology, normal waveforms and neural generators of the responses.

The book consists of five parts devoted respectively to a general description of EPs (part A: 78 pages), visual evoked potentials (VEPs, part B: 109 pages), auditory evoked potentials (AEPs, part C: 88 pages), SEPs (part D: 87 pages) and event-related and other potentials (part E: 16 pages). Obviously this latter section has not received as much attention as the four others, presumably because the author considers that the usefulness of late cognitive responses for routine neurological diagnosis is not yet fully established.

Part A is a superb, didactic and intelligent review of all basic concepts of EP methodology from differential amplification to signal filtering, sampling and averaging. In itself this part could be published separately as a guide booklet for technicians and neurologists involved in EP recording; it also represents the best available reference work for an academic and attractive teaching of signal processing principles.

Part B provides less information on VEPs to flash or pattern reversal stimulation than the similar chapter in Martin Halliday's book. For instance, the notion that the contralateral occipital P75-N105-P135 response to half-field stimulation might reflect cortical activity evoked by stimulation of the paramacular field is not even discussed. This part contains 16 interesting pages with well-selected references on the more unusual stimuli that have been tested to evoke visual responses

Part C is mainly devoted to brainstem auditory evoked potentials (BAEPs). The reviewer was puzzled by the importance given to interpeak delay between waves I and II and wave III splitting into two peaks for the routine interpretation of BAEPs. None of these BAEP patterns can be viewed as at all frequent, at least in the reviewer's experience. Surgical monitoring of BAEPs occupies only five lines—definitely too short.

Electroclinical correlations between cortical auditory disturbances, speech disorders and middle latency or late AEPs are not developed.

Part D on SEPs is clearly presented and nicely sums up recent data concerning early far-field scalp SEPs recorded with a noncephalic reference electrode as well as neck and scalp responses to upper limb stimulation obtained with more conventional recording procedures. Although illustrated in some figures, the frontal P22 and N30 potentials to median nerve or finger stimulation are not cited as usual components of the normal response. In spite of its real importance the notion that any scalp positive far-field component due to a moving source can be generated by a change of the electrophysical characteristics of the volume conductor is not discussed. The absence of a section devoted to EP mapping is regrettable.

The very few negative points cited above must not obscure the real qualities of Dr Spehlmann's book which is certainly among the best ever published on this topic since EPs became a routine procedure in clinical neurology. Presentation and printing by Butterworth is of a high professional standard. The foreseen success of this book will pay posthumous homage to Dr Spehlmann whose death occurred unexpectedly while the printing was still in progress.

FRANÇOIS MAUGUIERE

GABAergic Mechanisms in the Mammalian Periphery. Edited by Norman G. Bowery and Sandor L. Erdö. 1986. Pp. 336. New York. Raven Press. Price $98.00.

GABA (gamma-aminobutyric acid) is the major inhibitory neurotransmitter in the vertebrate brain. However, in invertebrates, this function extends into the peripheral nervous system. The question addressed in this book is the extent to which a peripheral extension of its central inhibitory action might also occur in mammals.

I have a personal interest in this question, because it was some eighteen years ago that one of the editors of this book (Dr Norman Bowery) and I started to look at the transport and actions of GABA in the mammalian sympathetic nervous system, in particular, in sympathetic ganglia. This was not from any prior conviction that GABA ought to be a transmitter in the sympathetic ganglion—indeed, quite the opposite: our starting point was that ganglia would provide an obviously *non*-GABAergic control for measurements of GABA uptake, localization and release in central nervous tissue. It was with some surprise, therefore, that we found a specific and well-developed transport system for GABA in the sympathetic ganglion which (it transpired) was localized to neuroglial satellite and Schwann cells (Bowery and Brown, 1972: *Nature, New Biology*, **238,** 89). Since Chet De Groat (1970: *Journal of Pharmacology and Experimental Therapeutics*, **172,** 384) had already shown (and we confirmed) that GABA could depolarize sympathetic ganglia via receptors essentially indistinguishable from those in the brain, a number of the criteria for a 'transmitter' or 'modulator' role seemed to have been met. Notwithstanding, we did not at that time regard this as evidence for a true functional role in the peripheral nervous system; instead, we regarded it more in the nature of a pharmacological curiosity, albeit of a very useful practical type as representing a simple paradigm of some of the features of GABA-transmitting central synapses. It is clear from the summary of more recent work on sympathetic ganglia by N. G. Bowery and D. R. Hill in this volume that there is no compelling reason to change this view in respect of this particular component of the peripheral nervous system.

It is equally clear, however, from other sections of this book that this rather nihilistic conclusion does not necessarily apply to other sectors of the peripheral nervous system—especially the intrinsic 'minibrains' of the gut and bladder. The question of a possible role of GABA in the gut goes back to the very early observations of Hobbiger (1958: *Journal of Physiology, London*, **142,** 147) on the actions of 'Factor I' on isolated mammalian intestinal preparations, and was resurrected by the demonstration of Jessen *et al.* (1979: *Nature, London*, **281,** 71) of a selective uptake of GABA by myenteric neurons in culture. In this book, K. R. Jessen, R. Mirsky and J. M. Hills update information on the uptake, localization and release of GABA in the enteric nervous system, and D. I. B. Kerr and J. Ong further review the evidence for a possible role of GABA in intestinal function. Two pieces of evidence seem particularly compelling: the immunocytochemical demonstration of the presence of endogenous GABA in enteric neurons and of its release in ileal tissue by field stimulation; and the ability of antagonists to GABA to modify some measures of gut motility, compatible with a degree of tonic release. It is envisaged that the effect of GABA released from the GABA-containing nerves is to modify the release of other transmitters such as acetylcholine by a presynaptic action. Similar, though less comprehensive, evidence for a comparable role of intrinsic GABAergic neurons in the intrinsic network in the bladder wall is summarized by K. Taniyama and C. Tanaka.

The highest concentrations of GABA in the periphery are found, most surprisingly, in the rat fallopian tube, whose levels exceed those in whole brain. Here it is localized not in the neurons but in the ciliated epithelium; whether it is synthesized in situ is not clear, since the tissue has a relatively low level of both GABA-synthesizing and inactivating enzymes. In spite of the fact that GABA can be released from stimulated oviduct and can cause it to contract, it seems difficult to assign it a conventional transmitter role in view of the above considerations. The possible role of GABA in the oviduct is addressed by the coeditor of this book, S. L. Erdö.

Outside the peripheral nervous system as such, the highest concentration of GABA and of its synthesizing enzyme, glutamic acid decarboxylase (GAD), is found in the pancreatic islets: this observation, together with a summary of the reported effects of GABA on hormonal release from the pancreas, is summarized in a very helpful way by Y. Okada. Likewise, S. Kuriyama and A. Tsujimoto summarize recent work on the possible role of GABA in the adrenal medulla, which also contains respectable levels of GABA and GAD and whose cells possess chloride channels linked to GABA receptors quite analogous to those in sympathetic and sensory neurons and to brain cells.

These are merely selected snippets: as will be apparent, this book is very broad-ranging and draws together a number of intriguing and sometimes perplexing observations whose significance is often more in prospect than in realization. In scientific terms this is by no means a disadvantage, since it raises many questions which might otherwise be ignored. Unlike many such tomes, the book is emphatically *not* a ragbag of symposium proceedings; instead, it is a well-produced and well-edited assembly of chapters by different authorities but with relatively little overlap. As such it provides a very useful overview of current knowledge in a neglected but growing area, which deserves a place in any respectable neuroscience library.

D. A. Brown

The Oculomotor and Skeletalmotor Systems: Differences and Similarities. *Progress in Brain Research*, Volume 64. Edited by H.-J. Freund, V. Büttner, B. Cohen and J. Noth. 1986. Pp. 432. Amsterdam: Elsevier. Price $118.50.

Although movements of the eye and the body are both motor acts, investigation of their neural basis has been conducted almost entirely separately and along different lines. There are good reasons why this has occurred and it is extremely useful at last to have a book which addresses the question of what are the common principles of organization as well as the differences between these two systems. This book is based on a meeting held in October 1984 at Schloss Hujenpoet, near Düsseldorf, to specifically address this question and was attended by scientists specializing in oculomotor or skeletomotor research. The organizers are to be congratulated on bringing together such a distinguished group of scientists and their contributions are divided into seven sections: final common pathway, sensory information used by the motor system, neuroanatomical substrates of premotor centres, specialized areas in motor control (supra- and infratentorial), functional organization of movements, adaptive control and psychophysical aspects and general concepts. Since the majority of contributors naturally concentrate on their field of expertise with a varying amount of reference to 'the other' system, a particularly useful feature is the three to four page summary of the discussions which took place during the meeting at the conclusion of each section.

The chapters are best when the contributor attempts to compare a particular aspect of oculomotor and somatomotor anatomy or physiology rather than rehearse previously published material. In this respect the chapter by Büttner-Ennever and Holstege on a comparison of the anatomy of premotor centres is particularly interesting. Since at the premotor level single cell recordings in the alert primate have provided a wealth of detailed data for the oculomotor system which have been denied the 'skeletomotorists' due to the technical difficulties of recording from the spinal cord in the moving animal it is useful to have such a comparison of the premotor anatomy.

Several chapters raise interesting questions concerning research strategy into motor behaviour. For example Wiesendanger considers the 'bottom-up' versus the 'top-down' approach, and Baker in a fascinating chapter warns against expecting to understand how a particular motor system works when the research into its function concentrates on highly evolved primates without attempts being made to gain insights into the range of its operation in other representative classes of vertebrate.

How then do the 'oculomotorists' fare at the hands of the 'skeletomotorists' in the oft-cited claim that what is learnt about the oculomotor system is of relevance to an understanding of other motor systems. Generally the views expressed in this book suggest that such a claim is invalid. This is mainly due to the problems of load and disturbance compensation which are applicable to the skeletomotor system but not the oculomotor system which has a constant load. However, as Robinson argues, at a higher level the planning and strategies of movement control for the two systems are probably not qualitatively different, although the oculomotor system is undoubtedly simpler.

The book is extremely well produced, as it should be for the price, and will be of particular value to anyone with an active interest in motor control.

Christopher Kennard

Neurohistochemistry: Modern Methods and Applications. Edited by Pertti Panula, Heikki Päivärinta and Seppo Soinila. *Neurology and Neurobiology*, Volume 16. 1986. Pp. 710. New York: Alan R. Liss. Price £39.00.

The volume entitled *Neurohistochemistry: Modern Methods and Applications* represents a comprehensive collection of 28 outstanding articles written by leading morphologists which summarize the current knowledge and progress concerning neurohistochemical techniques in different areas of the central and peripheral nervous system. The book is well presented and suitably illustrated with high quality black and white photomicrographs and would be a valuable addition to any library or personal collection. The editors have ensured a clear presentation of the chapters, each of which is divided into an introduction, which orientates the reader by outlining the previous work and background problems, followed by a material and methods section (where applicable) and a detailed description of current findings. The majority of chapters end with a summary of the data. Presentation of the work in such a manner ensures the book is of equal value to the undergraduate wishing to obtain an updated overview of neurotransmitter localization, and to the experienced researcher who will find the book offers much technical detail and an extensive bibliography to 1985.

This volume is dedicated to the late Olavi Eränkö, founder of the histofluorescence procedure for demonstration of catecholamines and who was known for his fundamental work on sympathetic ganglia cell types, in particular SIF cells (small intensely fluorescent cells). It is therefore fitting that many of the chapters relate to catecholamine localization and the sympathetic neuron.

The book is divided into three parts. The first, comprising 7 chapters, concerns new histochemical methods which are available for identification of transmitter or other chemically-defined structures. Topics include, identification of hitherto unknown brain-specific markers revealed by the approach of recombinant DNA technology, the development and application (conventional and novel) of monoclonal antibodies and the production and characterization of antibodies to amino acid transmitters and their synthesizing enzymes as well as monoamines. Finally, quantification and evaluation of coexistence of neuroactive substances using computer-assisted morphometry is discussed with neuropeptide Y/tyrosine hydroxylase-containing neurons in the hypothalamus as a working example.

The second section relates to differentiation, development and plasticity in the nervous system. Chromaffin and SIF cells are discussed extensively and the effects which various factors: neuronotropic, neurite promoting, hormones (e.g., glucocorticoids), etc., have on their phenotype expression reported. One chapter describes the use of intraocular transplantation in hypothyroid rats for study of the development of central monoamine neurons. These as well as astrocytes are markedly altered in thyroid hormone deficiency. The last chapter in this section reviews the ontogeny of 12 neuropeptides in the nervous system. The distribution and morphological description of many neurotransmitters/candidate neurotransmitters as well as their possible functions are dealt with in the final part, the largest section of the book (15 chapters). The application of successful raising and use of antibodies to such substances as neurotransmitters, their synthesizing enzymes as well as to receptors and modification of histochemical techniques is shown. Choline acetyl transferase, benzodiazepine receptors, histamine, NADPH-diaphorase and adenylate cyclase systems are described thoroughly in the brain. In the periphery, attention is paid to dopamine and GABA. The heterogeneous neurochemistry of the gut, eye and sympathetic neurons is the subject of further articles. Coexistence is reviewed and is a strong theme, as is the possible interaction between neuroactive substances.

It is apparent that methods for detection and analysis of neuronal pathways have reached a high degree of sophistication which would hardly have seemed possible 10 years ago. Further insights into the complexity of the nervous system have been revealed although in many cases the functional role of many neurochemicals remains unclear. Future developments, including visualization of transmitter mRNAs by in situ hybridization will hopefully lead to further enlightenment.

JULIA M. POLAK

ANNOUNCEMENTS

VIIth International Congress on Neuromuscular Diseases

This will be held in Munich, West Germany, on September 17–22, 1990. Further information may be obtained from the Secretary to the Congress, Dr F. Lehmann-Horn, Department of Neurology and Clinical Neurophysiology, Technical University, Möhlenstrasse 28, D-8000 München 80, West Germany

International Summer School of Brain Research

The Fifteenth International Summer School of Brain Research on 'Neurochemistry of functional neuroteratology. permanent effects of chemicals on the developing brain' will be held in Amsterdam, The Netherlands, on August 31–September 4, 1987. The intention of this Summer School is to present high level didactic reviews of important topics on the neurochemical changes underlying the lasting effects of chemicals on the developing brain to an audience of young researchers working in different branches of the neurosciences. For further information contact Mrs W. Chen-Pelt, Netherlands Institute for Brain Research, Meibergdreef 33, 1105 AZ Amsterdam ZO, The Netherlands (telephone 020-5665500).

Fyssen Foundation 1987 International Prize

The general aim of the Fyssen Foundation is to encourage all forms of scientific enquiry into cognitive mechanisms, including thought and reasoning, underlying animal and human behaviour, into their biological and cultural bases and into their phylogenetic and ontogenetic development For this purpose a substantial *International Scientific Prize* will be awarded for a major contribution to the progress of knowledge in the fields of research supported by the Foundation such as ethology, palaeontology, archaeology, anthropology, psychology, epistemology, logic and the neurosciences. The discipline for the 1987 Prize is Ethology—Animal Intelligence

Nominations for the 1987 Prize should be sent (15 copies) to the Secretariat of the Foundation, 194 rue de Rivoli, 75001 Paris and should include a curriculum vitae of the nominee, a list of his publications and a summary (four pages maximum) of the research upon which the nomination is based.

Nominations must be received by September 1, 1987

International Workshop on Craniofacial Trauma

Sponsored by the Australian Cranio-Maxillo-Facial Foundation, this workshop will be held in Adelaide, South Australia, on October 9–14, 1988. For information, contact Mrs D. Moody, Executive Office, 226 Melbourne Street, North Adelaide, SA 5006, Australia.

Travel Grants
For Young Neuroscientists

The Guarantors of *Brain* are prepared to consider applications for contributions towards travel costs from neuroscientists under the age of 40 working in the United Kingdom.

1. The primary purpose of such grants is to facilitate short visits to laboratories or departments of particular relevance to the applicant's research. Applications cannot be entertained without the following documents:
    (a) an abbreviated curriculum vitae and a list of any relevant publications;
    (b) statement of age and post currently held;
    (c) a concise account of the purpose of the proposed visit;
    (d) a recommendation from the head of department (where appropriate);
    (e) a letter of acceptance from the department to be visited;
    (f) a statement of costs likely to be incurred, and of other applications for funds that have been made. Advantage should always to taken of reduced air fares when available.
2. Applications will also be considered for contributions to the cost of attending specialized symposia of particular importance to the applicant's research. Documents as in (a), (b), (c), (d) and (f) above should be submitted at least three months before the date of the meeting, accompanied by a statement of what other applications for financial aid have been made and of any contributions by the symposium organization.
3. Only exceptionally will applications for assistance to attend larger international congresses be entertained.

Successful applicants will be expected to submit a brief report on the conclusion of their visit.

Four copies of all documents should be submitted to

Dr D. A. S. Compston,
Department of Neurology,
University Hospital of Wales,
Heath Park,
Cardiff CF4 4XW, UK

Reduced Subscription Rates

A reduced subscription rate (£20.00 per annum) is available to young subscribers under the age of 40 years, who are in a training post in clinical neurology or in the neurosciences in the UK. Applications for this special rate should be made to Dr D. A. S. Compston, Department of Neurology, University Hospital of Wales, Heath Park, Cardiff CF4 4XW, UK with a letter from the head of department confirming the applicant's eligibility.

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